### 7.3.933 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 ($MH^+$).

### 7.3.934 N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)

A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 ($MH^+$).

### 7.3.935 N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)

A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 ($MH^+$).

### 7.3.936 N4-(2,3-Dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)

A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TfOH was heated

for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 ($MH^+$).

**7.3.937 N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)**

A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 ($MH^+$).

**7.3.938 N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)**

The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 ($MH^+$).

**7.3.939 N4-(2,3-Dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)**

A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 ($MH^+$).

### 7.3.940 N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950349)

A solution of N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 ($MH^+$).

### 7.3.941 N4-(2,3-Dihydro-4-O-methyloxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950356)

A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.5%; MS (m/e): 465.10 ($MH^+$).

### 7.3.942 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950368)

A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 ($MH^+$).

### 7.3.943 N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950371)

A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J= 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J= 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 ($MH^+$).

### 7.3.944 N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950372)

A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 ($MH^+$).

### 7.3.945 N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)

A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 ($MH^+$).

### 7.3.946 N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)

A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 ($MH^+$).

### 7.3.947 N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 ($MH^+$).

### 7.3.948 N2,N4-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e): 489.29 ($MH^+$).

### 7.3.949 N2,N4-Bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)

A solution of N2,N4-bis(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J= 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50 ($MH^+$).

### 7.3.950 N2,N4-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)

A mixture of N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).

### 7.3.951 N2,N4-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)

A mixture of N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 ($M-H^-$).

### 7.3.952 N2,N4-Bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)

A mixture of N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 ($M-H^-$).

### 7.3.953 N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).

### 7.3.954 N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 ($MH^+$).

### 7.3.955 N4-(4-Benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with bortrifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H) 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 ($M-H^-$).

### 7.3.956 N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)

A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethylene oxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 ($MH^+$).

### 7.3.957 N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950388)

A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 ($MH^+$).

### 7.3.958 N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950389)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 ($M-H^-$).

### 7.3.959 N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J= 7.2 Hz), 7.31 (d, 1H, J= 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 ($MH^+$).

### 7.3.960 N4-(3-Methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)

A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-

methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.8%; MS (m/e): 510.41 ($MH^+$).

### 7.3.961 N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$). LCMS: purity: 96.2%; MS (m/e): 479.13 ($M-H^-$).

### 7.3.962 N4-[2,4-Dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945236)

N4-[2H-1,4-Benzoxazin-3(4H)-one-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (800 mg, 2.18 mmol) and phosphorus pentasulfide (800 mg, 1.80 mmol) were stirred in pyridine (5 mL) at 70 °C for 2h. The reaction solution was treated with 1N HCl solution to pH 5. The precipitation was collected with filtration, washed with water, dried to give N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine.

N4-[2H-1,4-Benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (400 mg, 1.04 mmol), glycine (500 mg) and triethylamine (0.5 mL) were stirred in methanol (10 mL) at 70 °C overnight. The undissolved salt was filtered off, washed with methanol. The filtrate was evaporated and redissolved in THF (5mL) and DMF (5 mL). To the solution were added EDC (200 mg), HOAt (200 mg) and diisopropylethylamine (0.2 mL). The reaction solution was stirred at 70 °C for 0.5 h. The

mixture was diluted with ethyl acetate (60 mL) and washed with water (2 x 60 mL). The organic layer was separated, dried, evaporated and purified by flash column chromatography (EtOAc/hexanes = 1:1, EtOAc) to give N4-[2,4-dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine as a white solid. $^1$H NMR ($CDCl_3$): δ 4.35 (t, J= 2.1 Hz, 2H), 4.92 (t, J= 2.1 Hz, 2H), 6.44 (dd, J= 1.5 and 8.1 Hz, 1H), 6.81 (m, 2H), 6.99 (s, 1H), 7.11 (m, 2H), 7.39 (m, 2H), 7.97 (d, J= 3.0 Hz, 1H), 8.02 (s, 1H), 8.57 (d, J= 2.4 Hz,1H); $^{19}$F NMR (282 MHz, $CDCl_3$): δ - 167.46; LCMS: ret. time: 13.71 min.; purity: 93.18%; MS (m/e): 407.10 ($MH^+$).

### 7.3.963 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine (R945237)

In a manner analogous to the preparation of N4-[2,4-dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (400 mg, 1.04 mmol) and β-alanine (500 mg) gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (acetone-$d_6$): δ 2.68 (t, J= 7.2 Hz, 2H), 3.71 (t, J= 7.2 Hz, 2H), 4.62 (t, J= 1.2 Hz, 2H), 6.42 (ddd, J= 1.2 and 2.4 and 7.5 Hz, 1H), 6.98-7.08 (m, 3H), 7.38 (t, J= 2.4 Hz, 1H), 7.62 (dd, J= 2.4 and 8.7 Hz, 1H), 7.96 (d, J= 3.3 Hz, 1H), 8.12 (s, 1H), 8.16 (s, 1H), 8.52 (d, J= 2.7 Hz, 1H), 8.65 (s, 1H); $^{19}$F NMR (282 MHz, acetone-$d_6$): δ - 168.04.

### 7.3.964 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine (R945242)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was treated with nitric acid (5 mL) and sulfuric acid (5 mL). The reaction mixture was heated to 70 °C for 30 min and then poured into ice-water. The solution was neutralized with sodium bicarbonate to pH 6. The yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers).

The mixture of nitrated compounds was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 30 min. The catalyst was filtered off. The filtrate was evaporated and treated with 2,4-dichloro-5-fluoropyrimidine (200 mg) in methanol (5

mL), water (5 mL). The reaction mixture was heated at 70 °C overnight, then evaporated. The residue was reacted with 3-methylaminocarbonylmethyleneoxyaniline (300 mg) in methanol (5 mL) and water (1 mL) at 100 °C overnight. The reaction mixture was diluted with 1N HCl solution (60 mL). The brown precipitation was collected by filtration, washed with water and dried to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 2.62 (d, J= 4.8 Hz, 3H), 4.33 (s, 2H), 4.63 (s, 2H), 6.48 (dd, J= 2.4 and 7.5 Hz, 1H), 7.11 (t, J= 8.1 Hz,1H), 7.27 (d, J= 7.8 Hz, 1H), 7.36 (s, 1H), 7.86 (d, J= 2.1 Hz, 1H), 7.97 (m, 1H), 8.12 (d, J= 3.6 Hz, 1H), 8.38 (d, J= 2.1 Hz, 1H), 9.33 (s, 1H), 9.46 (s, 1H), 11.18 (s, 1H); $^{19}$F NMR (282 MHz, DMSO-$d_6$): δ - 164.49; LCMS: ret. time: 13.16 min.; purity: 79.30%; MS (m/e): 440.16 ($MH^+$).

### 7.3.965 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine (R945263)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1g, 6.66 mmol) was refluxed with boron hydride methyl sulfide complex (2 mL) in THF (10 mL) for 30 min to give 2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 2H-pyrido[3,2-b]-1,4-oxazine was nitrated, reduced and reacted with 2,4-dichloro-5-fluoropyrimidine (400 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine as a gray solid. $^1$H NMR ($CDCl_3$): δ 2.91 (d, J= 4.8 Hz, 3H), 3.55 (t, J= 4.2 Hz, 2H), 4.24 (t, J= 4.5 Hz, 2H), 4.49 (s, 2H), 4.90 (br, 1H), 6.51 (dd, J= 2.7 and 8.1 Hz, 1H), 6.64 (s,1H), 6.90 (dd, J= 2.1 and 8.1 Hz, 1H), 7.08 (s, 1H), 7.14 (br, 1H), 7.18 (t, J= 8.1 Hz, 1H), 7.28 (d, J= 2.1 Hz, 1H), 7.51 (t, J= 2.1 Hz, 1H), 7.93 (d, J= 3.0 Hz, 1H), 7.95 (d, J= 2.4 Hz, 1H); LCMS: ret. time: 11.91 min.; purity: 100%; MS (m/e): 426.12 ($MH^+$).

### 7.3.966 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine (R921304)

2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (2.5 g) was dissolved in acetic acid (6 mL) and acetic anhydride (30 mL). Fuming nitric acid (3 mL) was added dropwise to the reaction solution in ice-bath. The reaction solution was stirred in ice-bath overnight.

Solution was poured into crashed ice. The light yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers). The mixture was crystallized from dichloromethane to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) as a light yellow solid.

6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) was reduced under hydrogenolysis conditions using 10% Pd-C in methanol (50 mL) and 1N HCl solution (10 mL) at 50 psi for 2 h. The catalyst was filtered off and washed with methanol and 1N HCl solution. The filtrate was evaporated to give 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one.

In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one was reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine as a beige solid. $^1$H NMR (DMSO-$d_6$): δ 2.63 (d, J= 4.5 Hz, 3H), 4.35 (s, 2H), 4.62 (s, 2H), 6.47 (dd, J= 1.8 and 8.1 Hz, 1H), 7.10 (t, J= 8.1 Hz,1H), 7.25 (d, J= 8.1 Hz, 1H), 7.37 (m, 2H), 7.59 (d, J= 8.4 Hz, 1H), 7.96 (d, J= 5.1 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 9.26 (s, 1H), 9.29 (s, 1H), 11.13 (s, 1H); $^{19}$F NMR (282 MHz, DMSO-$d_6$): δ - 163.20; LCMS: ret. time: 25.22 min.; purity: 97.55%; MS (m/e): 440.25 ($MH^+$).

### 7.3.967 5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine (R945299)

6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was refluxed with boron hydride methyl sulfide complex (1 mL) in THF (10 mL) for 30 min to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine was reduced and reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine as a gray solid. $^1$H NMR ($CD_3OD$): δ 2.81 (s, 3H), 3.48 (t, J= 4.5 Hz, 2H), 4.14 (t, J= 4.5 Hz, 2H), 4.44 (s, 2H), 6.60 (ddd, J= 1.5 and 2.7 and 7.5 Hz, 1H), 6.94

(d, J= 8.1 Hz, 1H), 7.14 (d, J= 3.0 Hz, 1H), 7.17 (t, J= 7.8 Hz, 1H), 7.40 (d, J= 8.9 Hz, 1H), 7.42 (t, J= 2.1 Hz, 1H), 7.92 (d, J= 3.3 Hz, 1H); $^{19}F$ NMR (282 MHz, $CD_3OD$): δ - 168.20; LCMS: ret. time: 25.49 min.; purity: 97.56%; MS (m/e): 426.23 ($MH^+$).

**7.3.968 N4-( 1,4-Benzoxazin-3-on-7-yl))-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908698):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-7-yl)pyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazin-3-on-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 7.30 (m, 2H), 7.09 (m, 4H), 6.5 (m, 1H), 4.6 (s, 2H) purity 95 %; MS (m/e): 368 (MH+)

**7.3.969 N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908699):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)] pyrimidineamine and 7-amino-1,4-benzoxazine-3-one were reacted to yield N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH+)

**7.3.970 N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-( (N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine (R908700):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-( (N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 8.00 (m, 1H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 95 % MS (m/e):439 (MH+)

**7.3.971 N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy)]-2,4-pyrimidinediamine (R908701):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(1,4-benzoxazin-3-onyl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were

reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 8.00 (m, 1H), 7.13 (m, 3H), 6.95 (m, 1H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 96 % MS (m/e): 439 (MH+)

**7.3.972 N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-( 3-hydroxyphenyl)-2,4-pyrimidinediamine (R908702):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-6-yl)phenylpyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-( 3-hydroxyphenyl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.22 (m, 2H), 7.03 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H) purity 98 %MS (m/e): 368 (MH+)

**7.3.973 5-Fluoro-N4-(3-hydroxyphenyl)- N2-(N-methyl-1,4-benzoxazine-3-on-6-yl)-2,4-pyrimidinediamine (R908703):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 6H), 6.55 (m, 1H), 4.64 (s, 2H), 3.18 (s, 3H) purity 96 %; MS (m/e): 382(MH+)

**7.3.974 5-Fluoro-N4-(3-hydroxyphenyl)-N2-( N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908704):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl)-N2-( N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.8.13 (d, 1H, J=4 Hz), 7.13 (m, 3H), 6.72 (m, 3H), 6.59 (m, 1H), 4.24 (m, 2H), 4.27 (s, 2H), 3.28 (m, 2H), 2.83 (m, 3H) purity 93 %; MS (m/e): 367 (MH+)

**7.3.975 5-Fluoro-N2-[ (N-methyl acetamido-2)-3-phenoxy]- N4-(N-methyl-1,4-benzoxazin-7-yl)- 2,4-pyrimidinediamine (R908705):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]- N4-(N-methyl-1,4-benzoxazin-7-yl)- 2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.13 (m, 5H), 6.75 (m, 2H), 4.44 (s, 2H), 4.27 (m, 2H), 3.22 (m, 2H), 2.83 (s, 3H), 2.63 (m, 3H) purity 96 %; MS (m/e): 439 (MH+)

**7.3.976 N2-( 1,4-Benzoxazin-7-yl )-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908706):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)]pyrimidineamine and 7-amino-1,4-benzoxazine were reacted to yield N2-( 1,4-Benzoxazin-7-yl )-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 7.95 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.02 (m, 4H), 6.42 (m, 2H), 4.17 (m, 2H), 3.33 (m, 2H) purity 96 %; MS (m/e): 353 (MH+)]

**7.3.977 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-( N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908707):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( N-methyl-1,4-benzoxazin-7-yl)pyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-( N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH+)

**7.3.978 5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine (R908708):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)pyrimidineamine and 7-amino-4-N-methyl-1,4-benzoxazine-3-one were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine. 1H

(DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 1H), 7.15 (m, 5H), 6.62 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H) purity 95 %; MS (m/e): 380 (MH+)]

**7.3.979 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine (R908709):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)] pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.43 (m, 2H), 7.19 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H), 3.25 (s, 3H) purity 95 %; MS (m/e): 382 (MH+)

**7.3.980 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908710):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-( 3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine. 1H (MeOD-d4) 8.20 (d, 1H, J=4 Hz), 7.43 (m, 3H), 6.90 (m, 2H), 6.75 (m, 1H), 4.25 (m, 2H), 3.25 (m, 2H), 2.85 (bs, 1 H) purity 96 %; MS (m/e): 382 (MH+)

**7.3.981 N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl) - pyrimidinediamine (R908711):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-ethoxyocarbonylmethyleneoxyaniline were reacted to yield N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl) -pyrimidinediamine $^1$H NMR (MeOD-d4): δ 8.2 (d, 1H, J=4 Hz), 7.15 (m, 4H), 6.84 (m, 2H), 6.62 (m, 1H), 4.65 (s, 2H), 4.15 (m, 4H), 3.28 (m, 2H), 1.19 (t, 3H. J=7 Hz) purity 94 %; MS (m/e): 439 ($MH^+$).

**7.3.982 (+/-)-5-Fluoro-N2-[ (N-methyl acetamido-2)-3-phenoxy]- N4-(2-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908712):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (+/-)-2-chloro-5-fluoro-N4-(2-methyl-1,4-benzoxazin-6-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were

reacted to yield (+/-)-5-Fluoro-N2-[ (N-methyl acetamido-2)-3-phenoxy]- N4-(2-methyl-1,4-benzoxazin-6-yl)- 2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 8.13 (m, 1H), 7.1 (m, 5H), 6.96 (m, 1H), 6.63 (m, 1H), 4.62 (m, 1H), 4.40 (s, 3H), 2.63 (m, 3H), 1.25 (m, 3H) purity 93 %; MS (m/e): 453 (MH+)

**7.3.983 N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl)phenyl]pyrimidinediamine (R908734):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-Amino-N-carbomethoxy-1,4-benzoxazine were reacted to yield N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl)phenyl]pyrimidinediamine 1H NMR (DMSO-d6): δ 8.23 (m, 1H), 7.20 (m, 1H), 7.14 (m, 4H), 6.95(m, 1H), 6.76 (m, 1H), 4.66 (s, 1H), 4.48 (s, 1H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 95 % MS (m/e): 454($MH^+$).

**7.3.984 N4-(1,4-Benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine (R909255):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-chloro-4-hydroxy-5-methylaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine $^1$H NMR (DMSO-d6): δ7.89 (d, 1H, J=4 Hz), 7.25 (m, 1H), 7.14 (m, 1H), 6.80 (m, 2H), 6.82 (m, 1H), 4.29 (s, 2H), 3.35 (m, 2H), 2.20 (s, 3H) purity 99 %; MS (m/e): 402 ($MH^+$).

**7.3.985 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine (R909259):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazinyl)]phenyl pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine 1H (DMSO-d6) 8.01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (m, 2H), 3.18 (m, 2H), 2.78 (s, 3H) 2.63 (m, 3H) purity 98 %; MS (m/e): 439 (MH+)

### 7.3.986 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine (R909260):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine 1H (DMSO-d6) 8.01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (s, 2H), 3.18 (s, 3H), 2.78 (s, 3H) 2.63 (m, 3H) purity 88%; MS (m/e): 453 (MH+)

### 7.3.987 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]-2,4-pyrimidinediamine (R909261):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)pyrimidinediamine 1H (DMSO-d6) 8.08 (d, 1H, J=4 Hz), 7.43 (m, 2H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) MS (m/e): 453 (MH+)

### 7.3.988 (+/-)-5-Fluoro-N4-(3-hydroxyphenyl]-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine (R909263):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-( 3-hydroxyphenyl)pyrimidineamine and 6-amino-2-methyl-1,4-benzothiazin-3-one were reacted to yield (+/-)-5-Fluoro-N4-(3-hydroxyphenyl]-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine $^1$H NMR (MeOD-d4): δ8.02 (d, 1H, J=4 Hz), 7.30 (m, 3H), 7.08 (m, 3H), 6.52 (m, 1H), 3.57 (m, 1H), 1.25 (m, 3H) purity 92 %; MS (m/e): 398 ($MH^+$).

### 7.3.989 5-Fluoro-N2-[3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-2,4-pyrimidinediamine (R909264):

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-[3-

hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.08 (d, 1H, J=4 Hz), 7.53 (m, 2H), 7.09 (m, 4H), 6.42 (m, 1H), 4.64 (s, 2H), 3.27 (s, 3H) purity 95 % MS (m/e): 382 (MH+)

**7.3.990 N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]pyrimidinediamine (R909265):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-Chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]pyrimidinediamine $^1$H NMR (DMSO-d6): δ 8.23 (m, 2H), 8.08 (d, J=4 Hz, 1H), 7.92 (m, 1H), 7.43 (m, 1H), 7.38(m, 2H), 7.18 (m, 1H), 6.99 (t, 1H), 6.41 (m, 1H), 5.43 (s, 2H) purity 92 %; MS (m/e): 534 ($MH^+$).

**7.3.991 N4-( 1,4-Benzoxazin-7-yl )-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909266):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-Benzoxazin-7-yl )-2-chloro-5-fluoro- pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-( 1,4-Benzoxazin-7-yl )-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.12 (m, 4H), 6.68 (m, 2H), 4.7 (s, 2H) 4.17 (m, 2H), 3.33 (m, 2H), 3.13 (m, 2H) 1.87 (m, 3H) purity 89 %; MS (m/e): 439 (MH+)

**7.3.992 N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine (R909267):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 3 Ethyl 6-Amino-(3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine were reacted to yield N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine 1H NMR (DMSO-d6): δ 8.18 (m, 1H), 8.04 (m, 1H), 7.38 (m, 1H), 7.22 (m, 1H), 7.04 (m, 2H), 6.96 (m, 1H), 6.53 (m, 1H), 5.42 (s, 2H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 92 % MS (m/e): 409 ($MH^+$).

### 7.3.993 N2-(1,4-Benzoxazin-3-on-6-yl)- 5-fluoro-N4-( 3-hydroxyphenyl)-2,4-pyrimidinediamine (R909268)

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 6-amino-1,4-benzoxazin-3-one were reacted to yield N2-(1,4-benzoxazin-3-on-6-yl)-5-fluoro-N4-( 6-(1,4-benzoxazinyl)]-)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-d6): δ 8.18 (d, 1H J= 4 Hz), 7.17 (m, 2H), 6.88 (m, 2H ), 6.80 (m, 1H ), 6.58 (m, 1H) 4.52 (s, 2H), 4.11 (m, 2H), 3.33 (m, 2H) purity: 97 %; MS (m/e): 409 ($MH^+$).

### 7.3.994 N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy) phenyl]-N4-(1,4-benzoxazin-6-yl)-5-fluoro--2,4-pyrimidinediamine (R909290)

In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-pyrimidinediamine and dimethylamine hydrochloride were reacted to yield N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy)phenyl] -N4-(1,4-benzoxazin-6-yl) -5-fluoro--2,4-pyrimidinediamine $^1$H NMR ($CD_3OD$): δ 7.8 (d, 1H), 7.4 (m, 1H), 7.05 (m, 2H), 7.0 (s, 1H), 6.8 (dd, 1H), 6.66 (d, 1H), 6.56 (dd, 1H), 4.35 (s, 2H), 4.18 (m, 2H), 3.25 (m, 2H), 2.8 (s, 6H); purity: 95 %; MS (m/e): 439 (MH+)

### 7.3.995 N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R909292)

To a solution in 2 mL THF at 0° Celsius containing 250 mg (0.59 mmol) of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 1.4 eq, 115 uL TEA, and catalytic DMAP was added 0.4 eq,70 mg of triphosgene. After 30 min 15 mL of aqueous ammonia and stirred for 30 min at RT. The THF was evaporated and the reaction was diluted with water, and the resulting precipitate collection by suction filtration. The crude precipitate was purified by preparative TLC (5% MeOH/EtOAc) to yield N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.83 (m, 1H), 7.42 (m, 1H), 7.12 (m, 2H), 7.08 (s, 1H), 6.84 (m, 1H), 6.66 (m, 1H), 6.48 (m, 1H), 4.30 (s, 2H), 4.15 (m, 2H), 3.22 (m, 2H), 2.82 (s, 3H); purity: 87 %; MS (m/e): 468 ($MH^+$).

**7.3.996 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909308):**

In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.00 (m, 1H), 7.43 (m, 2H), 7.05 (m, 1H), 6.82 (m, 2H), 6.68 (m, 1H), 6.41 (m, 1H), 4.80 (s, 2H), 4.18 (q, 2H), 3.74 (s, 2 H), 1.03 (t, 3H), 1.00 (s, 6H) purity 99 %; MS (m/e): 467 (MH+)

**7.3.997 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):**

In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.04 (d, 1H), 7.93 (m, 1H), 7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74 (s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH+)

**7.3.998 N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):**

In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[ 3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.04 (d, 1H), 7.93 (m, 1H), 7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74 (s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH+)

### 7.3.999 N4-(2,4-Diiodo-3-hydroxypheny)-5-fluoro-N2-(3-iodo-1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935221)

To 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (34.4 mg, 0.098 mmole) in ethanol (2.0 mL) and aq. $NH_4OH$ (2.0 mL), $I_2$ (0.126 g, 0.99 mmole atom) was added and stirred at room temperature overnight. Reaction mixture was concentrated, dissolved in EtOAc and treated with aq. hypo solution. Organic layer was separated, dried with anhydrous $Na_2SO_4$ and concentrated. The crude material was purified by silica gel column chromatography to provide N4-(2,4-diiodo-3-hydroxypheny)-5-fluoro-N2-[3-iodo-1-methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.86 (s, 1H), 9.51 (s, 1H), 9.12(s, 1H), 8.28 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.79 (s, 1H), 7.63 (s, 1H), 7.32 (d, 1H, J = 8.8 Hz), 7.37 (d, 1H, J = 8.8 Hz), 3.92 (s, 3H). LCMS: ret. time: 20.88 min.; purity: 91%; MS (*m/e*): 729 ($MH^+$).

### 7.3.1000 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935222)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methylindazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.17 (s, 1H), 9.13 (s, 1H), 8.10 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.85 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.46 (s, 2H), 6.87 (s, 2H, J = 8.8 Hz), 5.31 (s, 2H), 4.57 (sep, 1H, J = 5.8Hz), 3.65 (s, 3H), 1.25 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 ($MH^+$).

### 7.3.1001 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935223)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.16 (s, 1H), 9.14 (s, 1H), 8.13 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.89 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.9 Hz),

7.20 (dd, 1H, J = 2.9 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 5.32 (s, 2H), 4.22 (s, 4H), 3.65 (s, 3H). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 ($MH^+$).

### 7.3.1002 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935224)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.46 (s, 1H), 8.98 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 8.02 (d, 1H, J = 4.7 Hz), 7.98 (s, 2H), 7.66 (d, 1H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.46 (app s, 1H), 6.74 (d, 2H, J = 8.8 Hz), 4.96 (s, 2H), 4.46 (sept, 1H, J = 5.8 Hz), 2.58 (d, 3H, J = 4.7 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 18.22 min.; purity: 93%; MS (*m/e*): 450 ($MH^+$).

### 7.3.1003 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935225)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethyelnedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.47 (s, 1H), 8.99 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.01 (d, 1H, J = 4.7 Hz), 7.98 (d, 1H, J = 1.1 Hz), 7.66 (d, 1H, J = 8.8 Hz), 7.45 (dd, 1H, J = 1.1 and 8.8 Hz), 7.31 (d, 1H, J = 2.3 Hz), 7.01 (dd, 1H, J = 2.9 and 8.8 Hz), 6.66 (d, 1H, J = 8.8 Hz), 4.95 (s, 2H), 4.14 (s, 4H), 2.57 (d, 3H, J = 4.1 Hz). LCMS: ret. time: 15.55 min.; purity: 94%; MS (*m/e*): 450 ($MH^+$).

### 7.3.1004 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935237)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-

pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.40 (s, 1H), 9.19 (s, 1H), 9.17 (s, 1H), 8.23 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.90 (s, 1H), 7.47 (s, 2H), 7.25 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 8.2 Hz), 6.53 (d, 1H, J = 8.2 Hz), 5.31 (s, 2H), 3.64 (s, 3H). LCMS: ret. time: 15.82 min.; purity: 96%; MS (*m/e*): 409 ($MH^+$).

### 7.3.1005 N2, N4-Bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935238)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2, N4-bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.56 (s, 1H), 9.43 (s, 1H), 8.19 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 7.23 (dd, 1H, J = 1.7 and 8.8 Hz), 4.75 (t, 1H, J = 5.3 Hz), 4.68 (t, 1H, J = 5.3 Hz), 4.09-4.02 (m, 2H), 3.81-3.74 (m, 2H), 3.63-3.60 (m, 2H), 3.56-3.52 (m, 2H). LCMS: ret. time: 13.73 min.; purity: 90%; MS (*m/e*): 449 ($MH^+$).

### 7.3.1006 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935239)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.27 (s, 1H), 9.21 (s, 1H), 8.07 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.90 (qt, 1H, J = 4.7 Hz), 7.83 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.44 (s, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.98 (s, 2H), 4.57 (q, 1H, J = 5.8 Hz), 2.59 (d, 3H, J = 4.1 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.74 min.; purity: 94%; MS (*m/e*): 450 ($MH^+$).

### 7.3.1007 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935240)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.36 (br s, 2H), 8.06 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.99 (qt, 1H, J = 4.7Hz), 7.87 (s, 1H), 7.46 (s, 2H), 7.30-7.28 (m, 1H), 7.20-7.17 (m, 1H), 6.79 (d, 1H, J = 8.8 Hz), 4.99 (s, 2H), 4.22 (s, 4H), 2.59 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 15.06 min.; purity: 91%; MS (*m/e*): 450 ($MH^+$).

### 7.3.1008 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935242)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 4-isopropoxyaniline to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.58 (s, 1H), 10.09 (s, 1H), 8.23 (d, 1H, J = 5.3 Hz), 8.04 (s, 1H), 8.02 (s, 1H, J = 5.8 Hz), 7.68 –7.63 (m 1H), 7.58-7.55 (s, 1H), 7.30 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.8 Hz), 5.41 (s, 2H), 4.53 (sept, 1H, J = 5.8 Hz), 3.66 (s, 3H), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 19.30 min.; purity: 93%; MS (*m/e*): 451 ($MH^+$).

### 7.3.1009 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935248)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.42 min.; purity: 94%; MS (*m/e*): 423 ($MH^+$).

### 7.3.1010 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935249)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyridinamine was reacted with 3, 4-ethylenedioxyaniline to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.32 (s, 1H), 8.94 (s, 1H), 8.14 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 4.7 Hz), 8.01 (s, 1H), 7.65-7.57 (m, 2H), 7.23 (d, 1H, J = 1.7 Hz), 7.02 (dd, 1H, J = 1.9 and 8.8 Hz), 6.63 (d, 1H, J = 8.8 Hz), 5.38 (s, 2H), 4.14 (s, 4H), 3.66 (s, 3H). LCMS: ret. time: 18.94 min.; purity: 91%; MS (*m/e*): 451 ($MH^+$).

### 7.3.1011 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935250)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 3-aminophenol to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.34 (s, 1H), 9.16 (s, 1H), 8.25 (d, 1H, J = 4.7 Hz), 8.05 (d, 1H, J = 4.7 Hz), 8.02 (s, 1H), 7.65-7.57 (m, 2H), 7.10 (d, 2H, J = 5.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.28 (app d, 1H, J = 8.8 Hz), 5.37 (s, 2H), 3.66 (s, 3H). LCMS: ret. time: 17.87 min.; purity: 97%; MS (*m/e*): 409 ($MH^+$)

### 7.3.1012 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935251)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.93 (s, 1H), 9.21 (s, 1H), 7.97 (d, 1H, J = 4.1 Hz), 7.47 (d, 2H, J = 8.8 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.67 (d, 2H, J = 8.8 Hz), 6.02 (dd, 2H, J = 2.3 and 4.7 Hz), 4.48 (sept, 1H, J = 5.8 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 23.44 min.; purity: 90%; MS (*m/e*): 328 ($MH^+$).

### 7.3.1013 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935252)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 1-aminopyrrole to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.95 (s, 1H), 9.16 (s, 1H), 7.95 (d, 1H, J = 3.5 Hz), 7.16-7.12 (m, 2H), 6.69 (dd, 2H, J = 2.3 and 4.7 Hz), 6.61 (d, 1H, J = 8.8 Hz), 5.99 (dd, 2H, J = 2.3 and 4.7 Hz), 4.12-4.15 (m, 4H). LCMS: ret. time: 19.86 min.; purity: 92%; MS (*m/e*): 328 ($MH^+$).

### 7.3.1014 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935253)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.95 (s, 1H), 9.22 (s, 1H), 9.19 (s, 1H), 7.99 (d, 1H, J = 3.5 Hz), 7.22 (d, 1H, J = 8.2 Hz), 6.94 (br s, 1H), 6.89 (t, 1H, J = 8.2 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.38 (d, 1H, J = 8.2 Hz), 5.99 (t, 2H, J = 2.3 and 4.7 Hz). LCMS: ret. time: 18.23 min.; purity: 94%; MS (*m/e*): 286 ($MH^+$).

### 7.3.1015 5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935255)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H, J = 4.0 Hz), 7.79 (s, 1H), 7.59 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.57 (sept, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 20.90 min.; purity: 94%; MS (*m/e*): 423 ($MH^+$).

### 7.3.1016 5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935256)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.14 (s, 1H), 8.19 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.50-7.42 (m, 2H), 7.26 (d, 1H, J = 8.2 Hz), 7.12-7.06 (m, 2H), 6.52 (d, 1H, J = 8.2 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz). LCMS: ret. time: 15.97 min.; purity: 95%; MS (*m/e*): 381 ($MH^+$).

### 7.3.1017 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935258)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.20 (s, 1H), 8.93 (s, 1H), 8.12 (s, 1H), 8.02 (d, 1H, J = 3.5 Hz), 7.94 (s, 1H), 7.59 (s, 2H), 7.23 (d, 1H, J = 0.9 Hz), 7.02 (dd, 1H, J = 1.0 and 8.8 Hz), 6.64 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40 (t, 2H, J = 5.8 Hz), 4.15 (s, 4H), 3.78 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 18.07 min.; purity: 93%; MS (*m/e*): 423 ($MH^+$).

### 7.3.1018 5-Fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935259)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.31 (s, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.23 (s, 1H), 8.05 (d, 1H, J = 3.5 Hz), 7.96 (s, 1H), 7.60 (s, 2H), 7.10 (app s, 2H), 6.92 (t, 1H, J = 8.8 Hz), 6.31 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40

(t, 2H, J = 5.8 Hz), 3.79 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 16.09 min.; purity: 89%; MS (*m/e*): 381 ($MH^+$).

### 7.3.1019 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935261)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted 3, 4-ethyelenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 12.85 (s, 1H), 9.40 (s, 1H), 9.01 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.97 (s, 1H), 7.86 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.47 (dd, 1H, J = 2.3 and 8.8 Hz), 7.27 (d, 1H, J = 2.3 Hz), 7.07 (dd, 1H, J = 2.3 and 8.8 Hz), 6.64 (dd, 1H, J = 1.7 and 8.8 Hz), 4.14 (s, 4H). LCMS: ret. time: 15.90 min.; purity: 100%; MS (*m/e*): 379 ($MH^+$).

### 7.3.1020 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935262)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.80 (s, 1H), 10.49 (s, 1H), 8.35 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.78 (d, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.99-6.97 (m, 2H), 6.80 (s, 1H), 6.52-6.48 (m, 1H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 379 ($MH^+$).

### 7.3.1021 N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine (R935263)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.40 (s, 1H), 9.04 (s, 1H), 8.51 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.98 (d, 1H, J = 2.3 Hz), 7.67 (s, 1H), 7.53 (s, 1H), 7.41-7.36 (m, 1H), 7.20 (s, 1H), 7.10 (d, 1H, J = 8.8 Hz), 7.07 (s, 1H), 5.24 (s, 2H), 1.98 (s, 3H). LCMS: ret. time: 13.36 min.; purity: 90%; MS (*m/e*): 439 ($MH^+$).

### 7.3.1022 N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935264)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.62 (s, 1H), 9.19 (s, 1H), 8.61 (s, 1H,), 8.12 (s, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.50-7.45 (m, 2H), 7.26 (s, 1H), 1.98 (s, 3H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 385 ($MH^+$).

### 7.3.1023 5-Fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)- 2,4-pyrimidinediamine (R935266)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 4-isoporopoxyaniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.30 (s, 1H), 9.80 (s, 1H), 8.16 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.98 (s, 1H), 7.51 (s, 2H), 7.32 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J= 8.8 Hz), 4.51 (sept, 1H, J = 5.8 Hz), 1.22 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.65 min.; purity: 98%; MS (*m/e*): 379 ($MH^+$).

### 7.3.1024 N2-(3, 4-Ethyelenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935267)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyphenylaniline to produce N2-(3, 4-ethyelenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.20 (s, 1H), 9.61 (s, 1H), 8.13 (d, 1H, J = 5.3 Hz), 8.08 (s, 1H), 7.98 (s, 1H), 7.54-7.48 (m, 2H), 7.06 (d, 1H, J = 2.3 Hz), 6.90 (dd, 1H, J = 2.3 and 8.8 Hz), 6.72 (d, 1H, J = 8.8 Hz), 4.17 (s, 4H). LCMS: ret. time: 15.16 min.; purity: 100%; MS (*m/e*): 379 ($MH^+$).

### 7.3.1025 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935268)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-

pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.64 (s, 1H), 10.33 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 8.12 (s, 1H), 8.03 (s, 1H), 7.55 (dd, 2H, J = 1.7 and 8.8 Hz), 7.00 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.85 (d, 1H, J = 1.7 Hz), 6.53 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 12.80 min.; purity: 98%; MS (*m/e*): 337 ($MH^+$).

### 7.3.1026 5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine (R935269)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.64 (s, 1H), 9.82 (s, 1H), 8.20 (d, 1H, J = 4.6 Hz), 8.10 (s, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 7.57 (m, 2H), 7.13-7.6 (m, 3H), 6.56 (d, 1H, J = 8.8 Hz), 4.60 (s, 2H), 3.65 (s, 3H). LCMS: ret. time: 15.36 min.; purity: 94%; MS (*m/e*): 409 ($MH^+$).

### 7.3.1027 5-Fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935270)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 6-aminoindazoline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.35 (s, 1H), 9.19 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 8.12 (s, 1H), 8.01 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.60 (dd, 2H, J = 1.7 and 8.9 Hz), 7.51 (d, 1H, J = 8.9 Hz), 7.21 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.45 min.; purity: 95%; MS (*m/e*): 361 ($MH^+$).

### 7.3.1028 5-Fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl] -2,4-pyrimidinediamine (R935271)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 3-(*N*-

methylaminocarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.44 (s, 1H), 9.25 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.03 (d, 1H, J = 2.3 Hz), 7.90 (qt, 1H, J = 4.6 Hz), 7.69 (d, 1H, J = 1.2 Hz), 7.47 –7.42 (m, 1H), 7.33 (m, 1H), 7.26 (dd, 1H, J = 1.2 and 8.2 Hz), 7.12 (s, 1H), 7.09 (d, 1H, J = 1.7 Hz), 6.97 (t, 1H, J = 8.2H), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 5.25 (s, 2H), 4.26 (s, 2H), 2.61 (d, 3H, J = 4.6 Hz). LCMS: ret. time: 15.45 min.; purity: 97%; MS (*m/e*): 462 ($MH^+$).

#### 7.3.1029 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935276)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 4-isopropoxyaniline to produce 5-fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.69 (s, 1H), 9.03 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.30 (d, 2H, J = 9.3 Hz), 6.82 (t, 2H, J = 2.3 Hz), 6.58 (d, 2H, J = 9.3 Hz), 6.11 (t, 2H, J = 2.3 Hz), 4.41 (sept, 1H, J = 5.8 Hz), 1.18 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.21 min.; purity: 90%; MS (*m/e*): 328 ($MH^+$).

#### 7.3.1030 N2-(3, 4-Ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935277)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 11.63 (s, 1H), 9.94 (s, 1H), 8.23 (d, 1H, J = 4.7 Hz), 6.86 (m, 4H), 6.58 (d, 1H, J = 8.8 Hz), 6.12 (t, 2H, J = 2.3 Hz), 4.15 (s, 4H). LCMS: ret. time: 17.36 min.; purity: 96%; MS (*m/e*): 328 ($MH^+$).

#### 7.3.1031 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935278)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.68 (s, 1H), 9.04 (s, 1H), 9.00 (s, 1H), 8.08 (d, 1H, J = 4.11 Hz), 7.01 (d, 1H, J = 8.2

Hz), 6.84-6.75 (m, 4H), 6.22 (dd, 1H, J = 1.2 and 8.2 Hz), 6.08 (t, 2H, J = 2.3 Hz). LCMS: ret. time: 16.24 min.; purity: 94%; MS (*m/e*): 286 ($MH^+$).

### 7.3.1032 5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R935279)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(-methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 12.98 (s, 1H), 9.35 (s, 1H), 9.16 (s, 1H), 8.21 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.97 (s, 1H), 7.90 (qt, 1H, J = 4.7 Hz), 7.59 (dd, 1H, J = 8.8 Hz), 7.49 (d, 1H, J = 8.8 Hz), 7.32-7.28 (m, 2H), 7.03 (t, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 1.7 and 8.2 Hz), 4.31 (s, 2H), 2.61 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 12.92 min.; purity: 90%; MS (*m/e*): 408 ($MH^+$).

### 7.3.1033 5-Fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]- N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935280)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]- N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 11.45(s, 1H), 9.90 (s, 1H), 8.26 (d, 1H, J = 4.7 Hz), 7.07 (d, 1H, J = 8.2 Hz), 7.68 (d, 1H, J = 8.2 Hz), 6.94 (s, 1H), 6.85 (t, 2H, J = 2.3 Hz), 6.47 (dd, 1H, J = 2.3 and 8.2 Hz), 6.12 (t, 2H, J = 2.3 Hz), 4.64 (s, 2H), 3.68 (s, 3H). LCMS: ret. time: 16.24 min.; purity: 92%; MS (*m/e*): 358 ($MH^+$).

### 7.3.1034 5-Fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy) phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935281)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(-methoxycarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.73 (s, 1H), 9.21 (s, 1H), 8.11 (d, 1H, J = 4.1 Hz), 7.89 (qt, 1H, J

= 4.7 Hz), 7.14 (d, 1H, J = 8.2 Hz), 7.09 (s, 1H), 6.93 (t, 1H, J = 8.2 Hz), 6.84 (t, 2H, J = 2.3 Hz), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 6.09 (t, 2H, J = 2.3 Hz), 4.29 (s, 2H), 2.63 (s, 3H, J = 4.7 Hz). LCMS: ret. time: 16.16 min.; purity: 90%; MS (*m/e*): 357 ($MH^+$).

#### 7.3.1035 N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935286)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.37 (s, 1H), 9.20 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.87 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.33-7.21 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.34 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 3.93 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.04 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 ($MH^+$).

#### 7.3.1036 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935287)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.09 (d, 1H, J = 4.1 Hz), 8.01 (s, 1H), 7.85 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.32-7.20 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.20 (s, 4H), 3.27 (t, 2H, J = 6.4 Hz), 3.27 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 ($MH^+$). LCMS: ret. time: 22.09 min.; purity: 90%; MS (*m/e*): 437 ($MH^+$).

#### 7.3.1037 N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935288)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-

ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.02 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.34-7.22 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.33 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 23.10 min.; purity: 93%; MS (*m/e*): 464 ($MH^+$).

### 7.3.1038 N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(isopropoxyphenyl)-2,4-pyrimidinediamine (R935289)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.74 (s, 1H), 10.55 (s, 1H), 8.35 (d, 1H, J = 5.8 Hz), 7.98 (s, 1H), 7.77 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 7.16 (dd, 1H, J = 1.2 and 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 6.4 Hz), 4.31 (t, 2H, J = 6.4 Hz), 3.93 (qt, 2H, J = 7.0 Hz), 2.80 (t, 2H, J = 6.4 Hz), 1.22 (d, 6H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 26.84 min.; purity: 96%; MS (*m/e*): 479 ($MH^+$).

### 7.3.1039 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935290)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.31 (s, 1H), 9.22 (s, 1H), 8.08 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.85 (s, 1H), 7.62 (dd, 2H, J = 3.5 and 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.27 (d, 1H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 7.0 Hz), 4.49 (t, 1H, J = 5.3 Hz), 4.14 (t, 2H, J = 6.4 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 24.13 min.; purity: 97%; MS (*m/e*): 437 ($MH^+$).

**7.3.1040 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935291)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.32(s, 1H), 9.24 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 7.99 (s, 1H), 7.85 (s, 1H), 7.80 (qt, 1H, J = 4.7 Hz), 7.63 (d, 2H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.28 (d, 1H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.54 (sept, 1H, J = 5.8 Hz), 4.30 (t, 2H, J = 6.4 Hz), 2.55 (t, 2H, 7.4 Hz), 2.48 (d, 3H, J = 4.7 Hz), 1.24 (d, 6H, J = 6H). LCMS: ret. time: 23.68 min.; purity: 95%; MS (*m/e*): 464 ($MH^+$).

**7.3.1041 N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935292)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.35 (s, 1H), 10.21 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.90 (s, 1H), 7.63 (d, 1H, J = 8.8 Hz), 7.20-7.06 (m, 4H), 6.58 (d, 1H, J = 8.2 Hz), 4.33 (t, 2H, J = 6.4 Hz), 3.94 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.03 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 22.73 min.; purity: 94%; MS (*m/e*): 437 ($MH^+$).

**7.3.1042 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935293)**

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.38 (s, 1H), 9.35 (s, 1H), 9.26 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 1.7 Hz), 7.08 (t, 1H, J =

8.2 Hz), 6.49 (d, 1H, J = 8.2 Hz), 4.15 (t, 2H, J = 7.0 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.85 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 ($MH^+$). LCMS: ret. time: 20.37 min.; purity: 98%; MS (*m/e*): 395 ($MH^+$).

**7.3.1043 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935294)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.36 (s, 1H), 9.33 (s, 1H), 9.25 (s, 1H), 8.14 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.78 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.3 Hz), 7.07 (t, 1H, J = 8.2 Hz), 6.47 (d, 1H, J = 8.2 Hz), 4.32 (t, 2H, J = 6.4 Hz), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 93%; MS (*m/e*): 422 ($MH^+$).

**7.3.1044 N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(2-methoxycarbonylbenzofur-5-yl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine Purification of the crude gave two products.

**N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295):**

$^1H$ NMR (DMSO-$d_6$): δ 9.54 (s, 1H), 9.41 (s, 1H), 8.21 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.01 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.59 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 4.12 (t, 2H, J = 6.4 Hz), 3.91 (qt, 2H, J = 7.0 Hz), 3.88 (s, 3H), 2.72 (t, 2H, J = 6.4 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.67 min.; purity: 91%; MS (*m/e*): 519 ($MH^+$) and

**N4-[1-(2-carboxyethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935296)**

$^1$H NMR (DMSO-$d_6$): δ 9.54 (s, 1H), 9.39 (s, 1H), 8.23 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.00 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.58 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 1H, J = 8.2 Hz), 4.13 (t, 2H, J = 6.4 Hz), 3.88 (s, 3H), 2.67 (t, 2H, J = 6.4 Hz). LCMS: ret. time: 23.28 min.; purity: 91%; MS (*m/e*): 491 ($MH^+$).

**7.3.1045 5-Fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935297)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.00 (s, 1H), 9.90 (s, 1H), 8.70 (qt, 1H, J = 4.7 Hz), 8.24 (d, 1H, J = 4.1 Hz), 8.12 (d, 1H, J = 1.7 Hz), 7.911 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.71 (d, 2H, J = 1.7 and 8.8 Hz), 7.57 (dd, 1H, J = 3.5 and 8.8 Hz), 7.35 (s, 1H), 7.26 (dd, 1H, J = 3.5 and 8.8 Hz), 4.19 (t, 2H, J = 7.0 Hz), 2.53 (t, 2H, J = 7.0 Hz), 2.47 (d, 6H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 89%; MS (*m/e*): 503 ($MH^+$).

**7.3.1046 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935298)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-amino-2-methylindazoline were reacted to give 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.15 (s, 1H), 9.03 (s, 1H), 8.03-8.00 (m, 3H), 7.60 (dd, 2H, J = 4.1 and 8.8 Hz), 7.42 (d, 1H, J = 9.3 Hz), 7.31 (d, 1H, J = 9.3 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.57 (sept, 1H, J = 6.4 Hz), 4.08 (s, 3H), 1.26 (d, 6H, J = 6.4 Hz), LCMS: ret. time: 23.89 min.; purity: 98%; MS (*m/e*): 393 ($MH^+$).

### 7.3.1047 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935299)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.35 (s, 1H), 10.30 (s, 1H), 9.62 (br s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (d, 1H, J = 8.8 Hz), 7.17 (dd, 1H, J = 1.7 and 9.3 Hz), 7.08 (d, 2H, J = 5.3 Hz), 7.03 (s, 1H), 6.64-6.60 (m, 1H), 4.09 (s, 3H). LCMS: ret. time: 20.01 min.; purity: 97%; MS (*m/e*): 351 ($MH^+$).

### 7.3.1048 N4-(3, 4-Ethyelenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935300)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5- fluoro-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce N4-(3, 4-ethyelenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.64 (s, 1H), 10.62 (s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.21 (s, 1H), 7.77 (s, 1H), 7.58 (d, 1H, J = 9.3 Hz), 7.23-7.19 (m, 2H), 7.10 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.21 (s, 3H), 4.15 (s, 4H). LCMS: ret. time: 21.77 min.; purity: 92%; MS (*m/e*): 393 ($MH^+$).

### 7.3.1049 N2-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935301)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.15 (s, 1H), 9.13 (s, 1H), 8.10, (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.83 (s, 1H), 7.50 (s, 2H), 7.30 (d, 1H, J = 2.3 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 4.55 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.19 min.; purity: 93%; MS (*m/e*): 479 ($MH^+$).

### 7.3.1050 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935302)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.14 (s, 1H), 9.13 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.82 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.3 Hz), 7.18 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.59 (t, 1H, J = 6.4 Hz), 4.37 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 22.33 min.; purity: 100%; MS (*m/e*): 437 ($MH^+$).

### 7.3.1051 N4-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935303)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.50 (s, 1H), 10.46 (s, 1H), 9.62 (br s 1H), 8.28 (d, 1H, J = 5.8 Hz), 7.96 (s, 2H), 7.65 (d, 1H, J = 8.8 Hz), 7.36 (dd, 1H, J = 1.7 and 8.8 Hz), 7.15-7.08 (m, 3H), 6.67-6.64 (m, 1H), 4.59 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 23.68 min.; purity: 97%; MS (*m/e*): 437 ($MH^+$).

### 7.3.1052 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935304)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.20 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.46 (s, 2H), 7.24 (d, 1H, J = 8.2 Hz), 7.11-7.06 (m, 2H), 6.53 (d, 1H, J = 8.8 Hz), 4.56 (t,

1H, J = 4.7 Hz), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.92 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 ($MH^+$). LCMS: ret. time: 20.89 min.; purity: 98%; MS (*m/e*): 395 ($MH^+$).

**7.3.1053 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935305)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.19 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.84 (s, 1H), 7.82 (qt. 1H, J = 4.7 Hz), 7.46 (t, 2H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 7.11 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 8.2 Hz), 6.53 (t, 1H, J = 8.2 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.66 min.; purity: 95%; MS (*m/e*): 422 ($MH^+$).

**7.3.1054 N4-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935306)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 10.48 (s, 1H), 10.41 (s, 1H), 8.25 (d, 1H, J = 5.8 Hz), 7.93 (s, 1H), 7.84 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.36 (dd, 1H, J = 2.3 and 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.4 Hz), 4.57 (sept, 1H, J = 7.0 Hz), 3.96 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.23 (d, 6H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 27.39 min.; purity: 98%; MS (*m/e*): 479 ($MH^+$).

**7.3.1055 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935307)**

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-

pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.46 (t, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.60-4.52 (m, 2H), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 23.71 min.; purity: 98%; MS (*m/e*): 437 ($MH^+$).

### 7.3.1056 5-Fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935308)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.35 (s, 1H), 9.33 (s, 1H), 8.12 (d, 1H, J = 3.5 Hz), 7.99 (d, 1H, J = 1.7 Hz), 7.95 (s, 1H), 7.84 (s, 1H), 7.55-7.49 (m, 3H), 7.28 (d, 1H, J = 8.8 Hz), 6.62 (s, 1H), 5.46 (t, 1H, J = 5.8 Hz), 4.55 (d, 2H, J = 5.8 Hz), 4.45 (t, 1H, J = 4.7 Hz), 3.96 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 6.4 Hz), 1.76 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 20.86 min.; purity: 99%; MS (*m/e*): 449 ($MH^+$).

### 7.3.1057 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935309)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.12 (s, 1H), 9.11 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 3.5 Hz), 7.82 (s, 2H), 7.47 (s, 2H), 7.32-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.80 (d, 1H, J = 8.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 4.22 (s, 4H), 2.62 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 18.67 min.; purity: 100%; MS (*m/e*): 464 ($MH^+$).

**7.3.1058 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935310)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.18 (s, 1H), 9.09 (s, 1H), 8.08 (s, 1H), 8.02 (d, 1H, J = 4.1 Hz), 7.82 (qt, 1H, J = 4.7 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.57 (q, 2H, J = 5.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.47 (d, 3H, J = 4.7 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.14 min.; purity: 99%; MS (*m/e*): 464 ($MH^+$).

**7.3.1059 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935320)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR (DMSO-$d_6$): δ 9.36 (s, 1H), 9.18 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.56 (d, 1H, J = 8.2 Hz), 7.45 (d, 1H, J = 1.8 Hz), 7.43-7.38 (m, 1H), 7.36-7.34 (m, 1H), 7.30 (dd, 1H, J = 1.7 and 8.8 Hz), 7.20 (dd, 1H, J = 2.3 and 8.8 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.39 (s, 2H), 4.16 (s, 4H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 29.92 min.; purity: 80%; MS (*m/e*): 557 ($MH^+$).

**7.3.1060 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935321)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1H$ NMR

(DMSO-$d_6$): δ 9.37 (s, 1H), 9.31(s, 1H), 9.23 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.93 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 1.7 Hz), 7.40 (dd, 1H, J = 1.7 and 8.8 Hz), 7.33-7.27 (, 2H), 7.13 (t, 1H, J = 1.7 HZ), 7.03 (t, 2H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 1.7 and 8.2 Hz), 5.37 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 28.80 min.; purity: 92%; MS (*m/e*): 515 ($MH^+$).

#### 7.3.1061 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935322)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.60 (s, 2H), 8.11 (d, 1H, J = 4.1 Hz), 8.00-7.92 (m, 3H), 7.61-7.53 (m, 4H), 7.47-7.24 (m, 5H), 6.81 (d, 2H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 5.34 (s, 2H), 4.48 (sept, 1H, J = 5.9 Hz), 3.82 (s, 3H), 2.55 (s, 3H), 1.21 (d, 6H, J = 5.9 Hz). LCMS: ret. time: 30.57 min.; purity: 95%; MS (*m/e*): 696 ($MH^+$).

#### 7.3.1062 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935323)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. . $^1$H NMR (DMSO-$d_6$): δ 9.53 (s, 1H), 9.41 (s, 1H), 8.05 (d, 1H, J = 4.1 Hz), 7.96-7.90 (m, 3H), 7.55 (d, 1H, J = 8.8 Hz), 7.49 (dd, 1H, J = 7.6 Hz), 7.42-7.20 (m, 6H), 7.14-7.10 (m, 1H), 6.69 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 8.8 Hz), 5.33 (s, 2H), 4.10 (s, 4H), 3.77 (s, 3H), 2.50 (s, 3H). LCMS: ret. time: 32.11 min.; purity: 93%; MS (*m/e*): 696 ($MH^+$).

**7.3.1063 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935324)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.64 (s, 1H), 9.56 (s, 1H), 8.15 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.97 (d, 2H, J = 8.8 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 1.2 and 8.8 Hz), 7.47-7.23 (m, 6H), 7.11 (t, 1H, J = 1.7 Hz), 7.03 (t, 1H, J = 8.2 Hz), 6.62 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.36 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H). LCMS: ret. time: 29.79 min.; purity: 92%; MS (*m/e*): 654 ($MH^+$).

**7.3.1064 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935336)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.16 (s, 1H), 9.14 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1h), 8.04 (d, 1H, J = 3.5 Hz), 7.51 (d, 2H, J = 7.7 Hz), 7.49 (s, 1H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, J = 7.7 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.76 (d, 1H, J = 8.2 Hz), 5.58 (s, 2H), 4.22 (s, 4H), 3.92 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.91 min.; purity: 91%; MS (*m/e*): 557 ($MH^+$).

**7.3.1065 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935337)**

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR

(DMSO-$d_6$): δ 9.31 (s, 1H), 9.17 (s, 1H), 9.15 (s, 1H), 8.26 (s, 1H), 8.09 (d, 1H, J = 5.8 Hz), 8.08 (s, 1H), 7.52 (app t, 3H, J = 7.6 Hz), 7.42 (d, 1H, J = 8.2 Hz), 7.23 (d, 1H, J = 8.2 Hz), 7.08 (app s,1H), 7.03 (d, 1H, J = 8.2 Hz), 6.93 (d, 1H, J = 7.6 Hz), 6.43 (d, 1H, J = 8.2 Hz), 5.57 (s,2H), 3.90 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.51 min.; purity: 93%; MS (*m/e*): 515 ($MH^+$).

#### 7.3.1066 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935338)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-4-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.20 (s, 1H), 9.16 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.52-7.48 (m, 3H), 7.15 (d, 1H, J = 8.2 Hz), 6.86 (d, 2H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8 Hz), 5.56 (s, 2H), 4.46 (sept, 1H, J = 5.9 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 1.17 (d, 6H, J = 5.9 Hz). LCMS: ret. time: 11.94 min.; purity: 90%; MS (*m/e*): 557 ($MH^+$).

#### 7.3.1067 N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935339)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. . $^1$H NMR (DMSO-$d_6$): δ 9.57 (br s, 2H), 8.08 (d, 1H, J = 3.5 Hz), 8.01 (s, 1H), 7.99 (d, 1H, J = 1.0 Hz), 7.95 (s, 1H), 7.59-7.32 (m, 3H), 7.45-7.32 (m, 4H), 7.27-7.24 (m, 1H), 7.17-7.12 (m, 1H), 6.74 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 8.7 Hz), 5.58 (s, 2H), 4.15 (s, 4H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 11.33 min.; purity: 98%; MS (*m/e*): 696 ($MH^+$).

### 7.3.1068 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935340)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.57 (s, 1H), 9.48 (s, 1H), 8.13 (app s, 2H), 8.00 (d, 1H, J = 8.2 Hz), 7.94 (s, 1H), 7.59-7.32 (m, 7H), 7.18 (d, 1H, J = 8.2 Hz), 7.06 (app t, 3H, J = 8.8 Hz), 6.64 (d, 1H, J = 8.2 Hz), 6.55 (d, 1H, J = 8.2 Hz), 5.57 (s, 2H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 10.16 min.; purity: 97%; MS (*m/e*): 654 ($MH^+$).

### 7.3.1069 N4-(4-Chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935351)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.86 (s, 1H), 9.61 (s, 1H), 8.17 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.88 (s, 1H), 7.78 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.34 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 10.64 min.; purity: 94%; MS (*m/e*): 369 ($MH^+$).

### 7.3.1070 N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935352)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamime and 6-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.18 (s, 1H), 10.02 (s, 1H), 8.26 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.8 Hz), 7.65 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.19 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 10.80 min.; purity: 90%; MS (*m/e*): 355 ($MH^+$).

### 7.3.1071 N4-(4-Chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935353)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(4-chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.26 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.88 (s, 1H), 7.33-7.66 (m, 3H), 7.40 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 4.61 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.91 (t, 2H, J = 6.4 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 11.85 min.; purity: 95%; MS (*m/e*): 455 ($MH^+$).

### 7.3.1072 N4-(3-Chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935354)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-trifluoromethoxy-phenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(3-chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.63 (s, 1H), 9.30 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.10 (t, 1H, J = 2.3 Hz), 8.01 (s, 1H), 7.87 (s, 1H), 7.86 (d, 1H, J = 8.2 Hz), 7.57 (d, 1H, J = 9.4 Hz), 7.47 (t, 2H, J = 10.0 Hz), 4.56 (t, 2H, J = 6.9 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.9 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 14.4 min.; purity: 95%; MS (*m/e*): 539 ($MH^+$).

### 7.3.1073 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935355)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.63 (s, 1H), 9.35 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 8.01 (s, 1H), 7.86 (s, 1H), 7.79 (d, 1H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.47 (d, 1H, J = 8.2 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.30 min.; purity: 98%; MS (*m/e*): 404 ($MH^+$).

### 7.3.1074 5-Fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxypheny)-2,4-pyrimidinediamine (R935356)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give 5-fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxypheny)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 7.92 (s, 2H), 7.84 (d, 1H, J= 9.4 Hz), 7.75 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J= 9.4 Hz), 7.38 (d, 1H, J = 9.4 Hz), 7.08 (d, 1H, J = 8.8 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.13 min.; purity: 94%; MS (*m/e*): 419 ($MH^+$).

### 7.3.1075 N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935357)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.84 (s, 1H), 9.54 (s, 1H), 8.16 (d, 1H, J = 4.1 Hz), 8.00 (s, 2H), 7.87 (s, 1H), 7.55-7.32 (m, 4H), 3.99 (s, 3H). LCMS: ret. time: 11.26 min.; purity: 96%; MS (*m/e*): 415 ($MH^+$).

### 7.3.1076 N4-(3, 4-Difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935358)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluorophenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.50 (s, 1H), 9.27 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.08 (app s, 2H), 7.85 (s, 1H), 7.50 (app s, 3H), 7.37 (q, 1H, J = 9.4 Hz), 3.99 (s, 3H). LCMS: ret. time: 10.42 min.; purity: 90%; MS (*m/e*): 371 ($MH^+$).

### 7.3.1077 N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935359)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-

5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.79 (s, 1H), 9.45 (s, 1H), 8.19 (d, 1H, J = 4.1 Hz), 8.09 (t, 1H, J = 2.8 Hz), 8.00 (s, 1H), 7.85-7.81 (m, 2H), 7.51 (d, 1H, J = 8.8 Hz), 7.48-7.44 (m, 2H), 3.99 (s, 3H). LCMS: ret. time: 13.14 min.; purity: 92%; MS (*m/e*): 453 ($MH^+$).

### 7.3.1078 N2-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935360)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.55 (s, 1H), 9.26 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.95 (d, 1H, J = 8.2 Hz), 7.88 (s, 1H), 7.78 (s, 1H), 7.58 (dd, 1H, J = 8.8 and 7.4 Hz), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.56 (t, 2H, J = 7.0 Hz), 3.97 (q, 4H, J = 7.0 Hz), 2.88 (t, 2H, J = 7.0 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 13.22 min.; purity: 95%; MS (*m/e*): 505 ($MH^+$).

### 7.3.1079 5-Fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4- (3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935361)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-[1-[2(N-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4- (3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.55 (s, 1H), 9.25 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.96 (d, 1H, J = 8.2 Hz), 7.87 (s, 1H), 7.83 (qt, 1H, J = 4.9 Hz), 7.70 (s, 1H), 7.49 (dd, 2H, J = 8.2 and 9.4 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 10.00 min.; purity: 100%; MS (*m/e*): 490 ($MH^+$).

### 7.3.1080 5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935362)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.55 (s, 1H), 9.24 (s, 1H), 8.15 (d, 1H, J = 2.9 Hz), 8.05 (s, 1H), 7.92 (d, 1H, J = 7.6 Hz), 7.87 (s, 1H), 7.78 (s, 1H), 7.50 (s, 2H), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 7.6 Hz), 4.56 (t, 1H, J = 5.2 Hz), 4.38 (t, 2H, J = 7.0 Hz), 3.35 (dd, 2H, J = 5.2 and 7.0 Hz), 1.84 (qt, 2H, J = 7.0 Hz). LCMS: ret. time: 10.42 min.; purity: 97%; MS (*m/e*): 463 ($MH^+$).

### 7.3.1081 5-Fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935363)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine and 6-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.72(s, 1H), 9.60 (s, 1H), 9.42 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.06 (br s, 2H), 7.89 (s, 1H), 7.83 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.42 (t, 1H, J = 8.2 Hz), 7.27 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 12.17 min.; purity: 97%; MS (*m/e*): 405 ($MH^+$).

### 7.3.1082 5-Fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoro methoxyphenyl)-2,4-pyrimidinediamine (R935364)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamime and 5-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.85 (s, 1H), 9.54 (s, 1H), 9.23 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.93 (d, 1H, J = 8.2 Hz), 7.89 (s, 1H), 7.78 (s, 1H), 7.48-7.35 (m, 3H), 7.01 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 10.44 min.; purity: 98%; MS (*m/e*): 405 ($MH^+$).

### 7.3.1083 N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935365)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.85 (s, 1H), 9.43 (s, 1H), 9.19 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.87 (s, 1H), 7.82 (dd, 2H, J = 3.0 and 8.8 Hz), 7.42 (dd, 2H, J = 3.0 and 8.8 Hz), 7.31 (d, 2H, J = 8.8 Hz). LCMS: ret. time: 9.07 min.; purity: 91%; MS (*m/e*): 355 ($MH^+$).

### 7.3.1084 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935366)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.90 (s, 1H), 9.45 (s, 1H), 9.27 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 3.0 Hz), 8.02 (s, 1H), 7.87 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.44 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 11.65 min.; purity: 98%; MS (*m/e*): 439 ($MH^+$).

### 7.3.1085 5-Fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R935367)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3, 4,5-trimethoxyaniline were reacted by microwave heating at 180 $^{O}$C. Upon concentration of the ethanol and addition of 2N HCl provided 5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine as fine flakes of the solid. $^1$H NMR (DMSO-$d_6$): δ 9.59 (s, 1H), 9.25 (s, 1H), 8.09 (d, 1H, J = 3.5 Hz), 8.01 (dd, 2H, J = 5.3 and 1.2 Hz), 7.39 (dd, 2H, J = 3.1 and 8.8 Hz), 7.60-7.54 (m, 3H), 7.03 (d, 2H, J = 8.8 Hz), 6.94 (d, 2H, J = 3.1 Hz), 5.57 (s, 2H), 3.59 (s, 6H), 3.57 (s, 3H). LCMS: ret. time: 13.00 min.; purity: 97%; MS (*m/e*): 547 ($MH^+$).

### 7.3.1086 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935368)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 6-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.73 (s, 1H), 9.67 (s, 1H), 9.46 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.17 (app d, 1H, J = 8.8 Hz), 8.04 (br s, 1H), 7.97 (dt, 1H, J = 2.4 and 9.3 Hz), 7.89 (s, 1H), 7.58 (d, 1H, J = 8.8 Hz), 7.47 (d, 1H, J = 9.3 Hz), 7.27 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.08 min.; purity: 96%; MS (*m/e*): 439 ($MH^+$).

### 7.3.1087 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935369)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.62 (s, 1H), 9.29 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 2.4 Hz), 8.02 (app s, 1H), 7.88-7.82 (m, 3H), 7.53 (d, 1H, J = 9.3 Hz), 7.47 (d, 2H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.48 (t, 2H, J = 7.0 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 10.51 min.; purity: 99%; MS (*m/e*): 524 ($MH^+$).

### 7.3.1088 N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935370)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.62 (s, 1H), 9.28 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (s, 1H), 8.02 (s, 1H), 7.85 (s, 2H), 7.53 (t, 2H, J = 8.8 Hz), 7.46 (t, 1H, J = 8.8

Hz), 4.56 (t, 1H, J = 5.8 Hz), 4.38 (t, 2H, J = 6.4 Hz), 3.35 (dd, 2H, J = 5.8 and 6.4 Hz), 1.93 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 11.33 min.; purity: 99%; MS (*m/e*): 497 ($MH^+$).

### 7.3.1089 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935371)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.90 (s, 1H), 9.60 (s, 1H), 8.20 (d, 1H, J = 4.2 Hz), 8.06 (t, 1H, J = 2.3 Hz), 7.92 (s, 2H), 7.73 (d, 1H, J = 8.8 Hz), 7.51-7.40 (m, 3H). LCMS: ret. time: 9.83 min.; purity: 98%; MS (*m/e*): 390 ($MH^+$).

### 7.3.1090 N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935372)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 12.82 (s, 1H), 9.63 (s, 1H), 9.48 (s, 1H), 8.22 (d, 1H, J = 4.3 Hz), 8.15 (t, 1H, J = 2.3 Hz), 8.02 (s, 1H), 7.92-7.90 (m, 2H), 7.59 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.26 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 11.73 min.; purity: 99%; MS (*m/e*): 390 ($MH^+$).

### 7.3.1091 N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935373)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.40 (s, 1H), 10.11 (s, 1H), 8.25 (d, 1H, J = 4.5 Hz), 7.95 (s, 1H), 7.89 (app s, 2H), 7.49 (d, 1H, J = 8.8 Hz), 7.37 (app d, 3H, J = 8.2 Hz). LCMS: ret. time: 8.56 min.; purity: 99%; MS (*m/e*): 401 ($MH^+$).

### 7.3.1092 N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935374)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.53 (s, 1H), 9.52 (s, 1H), 8.21 (d, 1H, J = 4.5 Hz), 8.10 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.48 (dt, 1H, J = 2.3 and 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 7.21 (dd, 1H, J = 2.3 and 8.8 Hz). LCMS: ret. time: 11.29 min.; purity: 90%; MS (*m/e*): 401 ($MH^+$).

### 7.3.1093 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935375)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-methylindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.96 (s, 1H), 9.58 (s, 1H), 8.86 (s, 1H), 8.25 (dt, 1H, J = 3.9 and 8.8 Hz), 8.20 (d, 1H, J = 4.1 Hz), 8.04 (s, 1H), 7.55 (d, 1H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 8.95 min.; purity: 100%; MS (*m/e*): 370 ($MH^+$).

### 7.3.1094 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935376)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.78 (s, 1H), 9.41 (s, 1H), 8.88 (s, 1H), 8.24 (d, 1H, J = 8.2 Hz), 8.18 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.92 (s, 1H), 7.42 (app s, 3H). LCMS: ret. time: 7.87 min.; purity: 90%; MS (*m/e*): 356 ($MH^+$).

### 7.3.1095 N4-(6-Chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935377)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(6-chloro-3-pyridyl-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 10.37 (s, 1H), 10.04 (s, 1H), 8.78 (s, 1H), 8.28 (d, 1H, J = 4.8 Hz), 8.20 (dt, 1H, J = 2.8 and 8.8 Hz), 7.96 (s, 1H), 7.92 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.0 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.90 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 10.87 min.; purity: 94%; MS (*m/e*): 456 ($MH^+$).

### 7.3.1096 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935378)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.67 (s, 1H), 9.31 (s, 1H), 8.88 (s, 1H), 8.27 (dt, 1H, J = 3.0 and 8.8 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.88 (s, 1H), 7.83 (q, 1H, J = 5.3 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 4.53 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 5.3 Hz). LCMS: ret. time: 7.62 min.; purity: 89%; MS (*m/e*): 441 ($MH^+$).

### 7.3.1097 N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935379)

In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(6-chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$):. LCMS: ret. time: 8.02 min.; purity: 98%; MS (*m/e*): 414 ($MH^+$).

### 7.3.1098 N4-(2,6-Dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine (R935380)

In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,6-dimethoxy-3-pyridyl)-6-5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(2,6-dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine. $^1$H NMR (DMSO-$d_6$): δ 9.08 (s, 1H), 8.68 (s, 1H), 8.01 (d, 1H, J = 4.1 Hz), 7.96 (s, 1H), 7.76 (dd, 1H, J = 4.1 and 8.8 Hz), 7.65 (s, 1H), 7.37 (d, 1H, J = 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 6.46 (d, 1H, J = 8.2 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H). LCMS: ret. time: 9.57 min.; purity: 92%; MS (*m/e*): 396 ($MH^+$).

### 7.3.1099 Additional 2,4-Pyrimidinediamine

Compounds R008951, R008952, R008953, R008955, R008956, R008958, R070153 and R070790 (structures provided below) were purchased from Contact Services. Additional compounds whose structures are provided below were synthesized using methods similar to those described in the previous examples.

| | | | |
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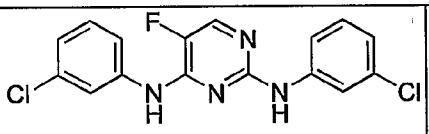
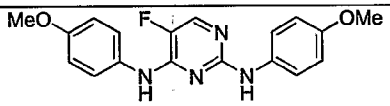
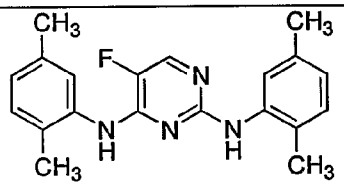
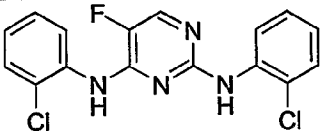
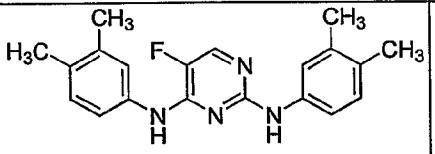
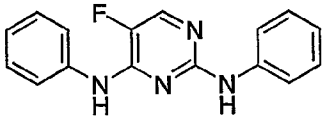
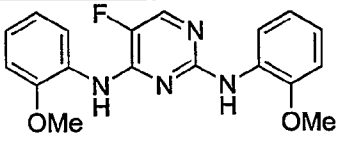
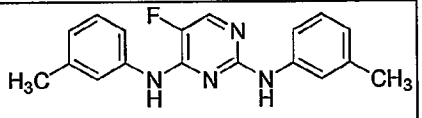
| R008951<br>R067962<br>R926209 |  | R088814<br>R926017 |  |
| R008952<br>R067963 |  | R088815 |  |
| R008953<br>R067964 |  | R091880 |  |
| R008955<br>R081166 |  | R092788 |  |

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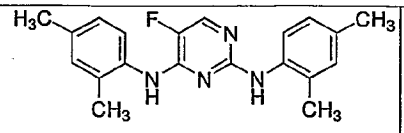
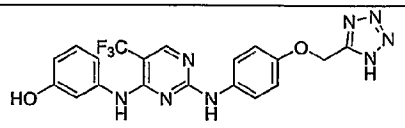
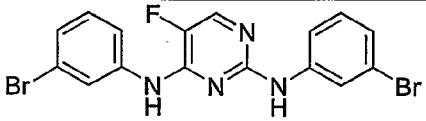
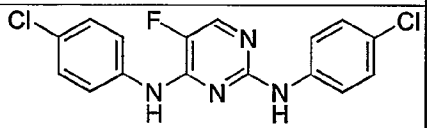
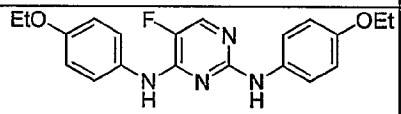
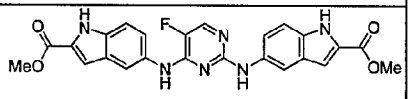
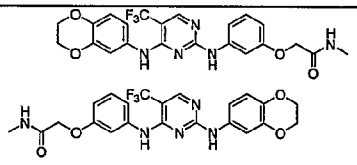
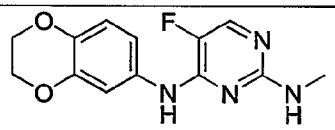
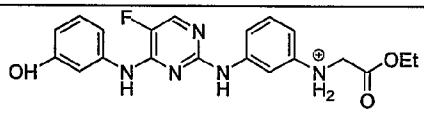
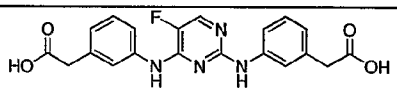
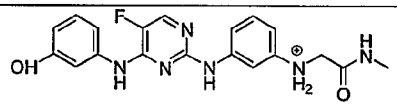
| R008956<br>R070791 |  | R920846 |  |
| R008958 |  | | |
| R070153 |  | | |
| R070790<br>R926036 |  | R926593 |  |
| R926736 |  | R950189 |  |
| | | R950216 |  |
| R935117 |  | R950218 |  |

### 7.3.1100 Synthesis of Intermediates, 2,4-Pyrimidinediamines and 2,4,6-Pyrimidinetriamines According to Schemes VIII and IX

A variety of intermediates and 2,4-pyrimidinediamine compounds were synthesized according to Schemes VIII and IX. Scheme VIII is exemplified by the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline to form a mixture of three compounds, which were separated and purified by chromotography. Scheme IX is exemplified by the reaction of 2,4,5,6-tetrachloridepyrimidine with 3,4-ethylenedioxyaniline to form a mixture of three compounds, which were separated and purified by chromotography.

**7.3.1101 Reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline**

**4,6-Dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (R926407)**

**N2,N4-Bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926408) and**

**N2,N4,N6-Tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (R926409)**

A mixture of 2,4,6-trichloroaniline (0.183g, 1 mmol) and 3-hydroxyaniline (0.327g, 3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with $H_2O$, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr, 4,6-dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (**R926407**),: $^1$H NMR ($CDCl_3$): δ 7.16 (t, 1H, J= 8.1 Hz), 6.78 (m, 2H), 6.64 (dd, 1H, J= 1.2 and 8.1 Hz), 6.58 (s, 1H); LCMS: ret. time: 25.08 min.; purity: 99%; MS (m/e): 256 ($M^+$); bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (**R926408**), $^1$H NMR ($CD_3OD$): δ 7.21 (m, 1H), 7.14-7.03 (m, 5H), 6.50 (m, 1H), 6.44 (m, 1H), 6.16 (s, 1H); LCMS: ret. time: 25.14 min.; purity: 99%; MS (m/e): 329 ($M^+$); and tris-SNAr product, N2,N4,N6-tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (**R926409**), $^1$H NMR ($CD_3OD$): δ 7.29 (m, 1H), 7.12-7.05 (m, 5H), 7.02 (m, 2H), 6.88 (dd, 2H, J= 1.2 and 8.1 Hz), 6.46 (dd, 1H, J= 1.5 and 8.1 Hz), 6.41 (dt, 1H); LCMS: ret. time: 20.49 min.; purity: 94%; MS (m/e): 402 ($MH^+$).

**7.3.1102 N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926411)**

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline, the reaction of 2,4,6-trichloropyrimidine with methyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.65 (bs, 1H), 7.40 (bd, 4H), 6.82 (bd, 4H), 6.00 (s, 1H), 6.62 (bs, 4H), 3.78 (bs, 6H); LCMS: ret. time: 29.87 min.; purity: 98%; MS (m/e): 473 ($MH^+$).

**7.3.1103 Reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline**

**4,6-Dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (R926515)**

**N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926245)**

**N2,N4,N6 -Tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (R926516)**

A mixture of 2,4,6-trichloroaniline (1 mmol) and 3,4-ethylenedioxyaniline (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with $H_2O$, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the Mono-SNAr product, 4,6-dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (**R926515**). $^1$H NMR ($CD_3OD$): δ 7.05 (s, 1H), 6.83 (m, 2H), 6.45 (bs, 1H), 4.20 (bs, 4H); LCMS: ret. time: 29.75 min.; purity: 96%; MS (m/e): 298 ($M^+$); Bis-SNAr product, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (**R926245**):

$^1$H NMR ($CDCl_3$): δ 7.23 (d, 1H, J= 3 Hz), 6.90-6.70 (m, 6H), 6.02 (s, 1H), 4.26 (bs, 4H), 4.23 (m, 4H); LCMS: ret. time: 31.34 min.; purity: 95%; MS (m/e): 413 ($MH^+$) and Tris-SNAr product, N2,N4,N6 -tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (**R926516**)

$^1$H NMR ($CD_3OD$): δ 7.16 (d, 1H, J= 3Hz), 7.05 (bd, 1H), 6.99-6.90 (m, 3H), 6.80-6.70 (m, 4H), 6.03 (s, 1H), 4.22 (s, 4H), 4.20 (s, 8H); LCMS: ret. time: 27.72 min.; purity: 61%; MS (m/e): 528 ($M^+$).

### 7.3.1104 Reaction of 2,4,6-trichloropyrimidine with ethyl-4-aminophenoxyacetate

**4,6-Dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (R926549)**

**2,6-Dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (R926550)**

A mixture of 2,4,6-trichloroaniline (1 mmol) and ethyl 2-aminoacetate (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with $H_2O$, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr product, 4,6-dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (**R926549**). $^1$H NMR ($CDCl_3$): δ 6.67 (s, 1H), 5.85 (bs, 1H), 4.23 (q, 2H, J= 7.2 Hz), 4.19 (s, 2H), 1.29 (t, 3H, J= 7.2 Hz);

LCMS: ret. time: 26.18 min.; purity: 100%; MS (m/e): 250 ($MH^+$); and Mono-SNAr product, 2,6-dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (**R926550**): $^1H$ NMR ($CDCl_3$): d 6.37 (bs, 1H), 4.28 (q, 2H, J= 6.9 Hz), 4.19 (bs, 2H), 1.31 (t, 3H, J= 7.2 Hz)

**7.3.1105 6-Chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine (R926555)**

In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of ethyl 4-aminophenoxyacetate with methyl 2-aminoacetate gave 6-chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine. $^1H$ NMR ($CD_3OD$): δ 7.40 (d, 2H, J= 8.7 Hz), 6.86 (d, 2H, J= 9.3 Hz), 5.97 (s, 1H), 4.64 (s, 2H), 4.26 (q, 2H, J= 7.2 Hz), 4.14 (q, 2H, J= 6.9 Hz), 4.05 9s, 2H), 1.25 (m, 6H); LCMS: ret. time: 26.21 min.; purity: 93%; MS (m/e): 409 ($MH^+$).

**7.3.1106 Reaction of 3,4-ethylenedioxyaniline with 2,4,5,6-tetrachloropyrimidine.**

**N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926466)**

**N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926467) and**

**N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926468)**

A mixture of 3,4-ethylenedioxyaniline (0.775 g, 5 mmol) and 2,4,5,6-tetrachloropyrimidine (0.434 g, 2 mmol) in the presence of DIPEA (1.043 mL, 6 mmol) in EtOAc (10 mL) was heated at 80 °C for 3 days. The reaction was diluted with water (50 mL), acidified (2N HCl) and extracted with EtOAc (3 x 50 mL). The residue obtained after removal of solvent was chromatographed using 5-30% EtOAc/hexanes to obtain three products viz. N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926466**): $^1H$ NMR ($CDCl_3$): δ 7.18 (d, 1H, J= 2.7 Hz), 6.92 (dd, 1H, J= 2.1 and 8.7 Hz), 6.87 (d, 1H, J= 9 Hz); LCMS: ret. time: 33.53 min.; purity: 100%; MS(m/e): 292 ($MH^+$); N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926467**): $^1H$ NMR ($CDCl_3$): δ 7.11 (d, 1H, J= 2.4 Hz), 7.06 (d, 1H, J= 2.1 Hz), 7.04 (s, 1H0, 6.94 (m, 2H), 6.84 (d, 1H, J= 8.1 Hz), 6.76 (bd, 2H, J= 8.7 Hz), 4.27 (bs, 4H), 4.24 (bs, 1H); LCMS: ret. time:

26.54 min.; purity: 87%; MS(m/e): 364 ($MH^+$); and N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926468**): $^1H$ NMR ($CDCl_3$): δ 7.07 (t, 1H, J= 2.4 Hz), 6.99 (s, 2H), 6.83 (dd, 2H, J= 2.4 and 8.7 Hz), 6.75 (dd, 2H, J= 1.8 and 9 Hz), 4.19 (bs, 4H); LCMS: ret. time: 34.70 min.; purity: 99%; MS(m/e): 365 ($MH^+$).

**7.3.1107 Reaction of 2,4,5,6-tetrachloropyrimidine with ethyl-4-aminophenoxyacetate**

**N4-(4-Ethoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926568)**

**N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926569)**

**N2,N5-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (R926570)**

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with ethyl 4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-ethoxycarbonyl methyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926568**): $^1H$ NMR ($CDCl_3$): δ 7.46 (dd, 2H, J= 2.4 and 6.9 Hz), 7.3 (s, 1H), 6.95 (dd, 2H, J= 2.4 and 6.9 Hz), 4.63 (s, 2H), 4.28 (q, 2H, J= 7.2 Hz), 1.30 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 30.62 min.; purity: 99%; MS (m/e): 378 ($MH^+$); Bis-SNAr product, N2,N4-bis((4-ethoxycarbonylmethylene oxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926569**): $^1H$ NMR ($CDCl_3$): δ 7.42 (d, 2H, J= 9 Hz), 7.35 (d, 2H, J= 8.7 Hz), 6.90 (d, 2H, J= 9Hz), 6.83 (d, 2H, J= 8.7 Hz), 4.67 (s, 2H), 4.60 (s, 2H), 4.28 (2q, 4H, J= 4.8 Hz), 1.31 (2t, 6H, J= 6.3 Hz); LCMS: ret. time: 33.09 min.; purity: 85%; MS (m/e): 537 ($MH^+$) and Bis-SNAr product, N2,N5-bis((4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (**R926570**): $^1H$ NMR ($CDCl_3$): δ 7.45 (d, 4H, J= 8.7 Hz), 6.92 (d, 4H, J= 9Hz), 6.85 (s, 1H), 4.61 (s, 4H), 4.26 (q, 4H, J= 6.9 Hz), 1.30 (t, 6H, J= 7.2 Hz); LCMS: ret. time: 31.66 min.; purity: 97%; MS (m/e): 535 ($MH^+$).

**7.3.1108 Reaction of 2,4,5,6-tetrachloropyrimidine with tert-Butyl-4-aminophenoxyacetate, N4-(4-tert-Butoxyoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926575), N2,N4-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926576) and N4,N6-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926577)**

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-tert-butoxyoxycarbonyl methyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926575**): $^1$H NMR ($CDCl_3$): δ 7.45 (dd, 2H, J= 2.4 and 7.2 Hz), 6.93 (dd, 2H, J= 2.4 and 7.2 Hz), 4.52 (s, 2H); LCMS: ret. time: 32.56 min.; purity: 100%; MS (m/e): 402 ($MH^+$); Bis-SNAr product, N2,N4-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926576**): $^1$H NMR ($CDCl_3$): δ 7.42 (d, 2H, J= 9 Hz), 7.35 (d, 2H, 9.3 Hz), 7.08 (s, 1H), 6.90 (d, 2H, J= 9.3 Hz), 6.82 (d, 2H, J= 8.7 Hz), 4.53 (s, 2H), 4.49 (s, 2H), 1.50 (s, 9H), 1.49 (s, 9H); LCMS: ret. time: 36.04 min.; purity: 92%; MS (m/e): 591 ($MH^+$) and Bis-SNAr product, N4,N6-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926577**): $^1$H NMR ($CDCl_3$): δ 7.43 (d, 4H, J= 8.7 Hz), 6.90 (dd, 4H, J= 9.3 Hz), 4.50 (s, 2H), 1.49 (s, 18H); LCMS: ret. time: 35.31 min.; purity: 100%; MS (m/e): 591 ($MH^+$).

**7.3.1109 Reaction of 2,4,5,6-tetrachloropyrimidine with 3-hydroxyaniline, N4-(3-Hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926590), N2,N4-Bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926591) and N4,N6-Bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926592)**

In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(3-hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926590**): $^1$H NMR ($CDCl_3$): δ 7.38 (bs, 1H), 7.32 (t, 1H, J= 2.4 Hz), 7.22 (s, 1H), 7.01 (dd, 1H, J= 1.2 and 8.1 Hz), 6.68 (dd, 1H, J= 1.8 and 8.1 Hz); LCMS: ret. time: 26.09 min.; purity: 99%; MS (m/e): 292 ($MH^+$); Bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926591**): $^1$H NMR

($CDCl_3$): δ 7.45 (s, 1H), 7.30 (t, 1H, J= 2.4 Hz), 7.18 (t, 1H, J= 2.4 Hz), 7.07 (t, 1H, j= 6.6 Hz), 6.98 (t, 1H, J= 8.1 Hz), 6.75 (m, 2H), 6.54 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: ret. time: 26.54 min.; purity: 87%; MS (m/e): 364 ($MH^+$); and Bis-SNAr product, N4,N6-bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926592**): $^1H$ NMR ($CDCl_3$): δ 7.34 (t, 2H, j= 2.4 Hz), 7.21 (t, 2H, J= 7.5 Hz), 6.98 (m, 4H), 6.60 (m, 2H); LCMS: ret. time: 25.38 min.; purity: 73%; MS (m/e): 364 ($MH^+$).

#### 7.3.1110 N2,N4-Bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926595)

The reaction of N2 N4-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (18 mg, 0.05 mmol) with sodium thiomethoxide (10 mg, 0.15 mmol) in absolute EtOH (1 mL) was heated at 80 °C for 3 days, diluted with $H_2O$, extracted with EtOAc (3 x 10 mL), and solvent was evaporated to obtain the N2 N4-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**). $^1H$ NMR ($CD_3OD$): δ 7.40-7.2 (m, 2H), 7.20-6.80 (m, 3H), 6.67 (m, 1H), 6.45-6.30 (m, 2H), 2.4 (s, 3H); LCMS: ret. time: 27.78 min.; purity: 80%; MS (m/e): 376 ($MH^+$).

#### 7.3.1111 N2,N4-Bis(3,4-ethyelenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926475)

In like manner to the preparation of N2 N4-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**), the reaction of N2,N4-bis(3,4-ethyelenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine gave N2,N4-bis(3,4-ethyelenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine. $^1H$ NMR ($CDCl_3$): δ 7.10 (bd, 2H), 7.00-6.00 (m, 4H), 4.23 (s, 4H), 4.10 (s, 4H), 2.60 (s, 3H); LCMS: ret. time: 36.14 min; purity: 100%; MS (m/e): 459 ($MH^+$).

#### 7.3.1112 6-Chloro N4-(3-hydroxyphenyl)-4-pyrimidineamine (R926530)

The reaction of 4,6-dichloropyrimidine with excess 3-hydroxyaniline in MeOH at 80 0 °C for 24 h followed by dilution with water and acidification gave the crude product which was purified by silica gel column chromatography to obtain 6-chloro N4-(3-hydroxyphenyl)-4-pyrimidineamine. $^1H$ NMR ($CD_3OD$): δ 8.36 (d, 1H, J= 1.2 Hz), 7.15 (t, 1H, J= 8.4 Hz), 6.93 (dd, 1.2 and 8.1 Hz), 6.74 (d, 1H, J= 1.2 Hz), 6.55 (dd, 1.8 and 8.1 Hz); LCMS (m/e): ret. time: 19.75 min.; purity: 99%; MS (m/e): 222 ($MH^+$).

### 7.3.1113 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925784)

A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine (20 mg, 0.044 mmol) and phenylboronic acid (6.9 mg, 0.057 mmol) in DME (1 mL) was prepared in a sealed tube and purged with $N_2$. Tetrakis(triphenylphosphine) palladium(0) (0.002 mmol) was added, and the reaction tube sealed and heated at 80 °C overnight. After cooling, the reaction mixture was diluted with EtOAc, washed with 1N NaOH and brine, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC (40% EtOAc/hexanes) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.77 (s, 1H), 7.52-7.36 (m, 5H), 7.10 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 2.4 Hz), 6.93 (dd, 1H, J= 2.4 and 8.7 Hz), 6.87 (dd, 1H, J= 2.4 and 8.7 Hz), 6.73 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.7 Hz), 4.23-4.20 (m, 8H); LCMS: ret. time: 25.38 min.; purity: 100 %; MS (m/e): 455 ($MH^+$).

### 7.3.1114 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine (R925785)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and furan-2-boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 8.13 (s, 1H), 7.61 (d, 1H, J=1.8 Hz), 7.12 (d, 1H, J= 2.4 Hz), 7.08 (d, 1H, J= 2.4 Hz), 6.93 (td, 2H, J= 2.4 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 6.58 (d, 1H, J= 2.4 Hz), 6.54 (dd, 1H, J= 1.8 and 3.6), 4.24 (s, 4H), 4.20 (bs, 4H); LCMS: ret. time: 15.03 min.; purity: 88 %; MS (m/e): 445 ($MH^+$).

### 7.3.1115 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine (R925786)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-d6): δ 8.99 (bs, 1H), 8.05 (bs, 1H), 7.85 (s, 1H), 7.50-7.42 (m, 4H), 7.23 (bs, 1H), 7.10 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (t, 1H, J= 2.4 Hz), 7.00-6.94 (m, 1H), 6.73 (d, 1H, J= 8.7 Hz), 6.63 (d, 1H, J= 8.7 Hz); LCMS: ret. time: 16.12 min.; purity: 86 %; MS (m/e): 490 ($MH^+$).

### 7.3.1116 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine (R925787)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.77 (s, 1H), 7.45-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.09 (d, 1H, J= 2.4 Hz), 7.01 (d, 1H, J= 2.4 Hz), 6.92 (dd, 1H, J= 2.4 and 9.0 Hz), 6.86 (dd, 1H, J= 2.4 and 8.7 Hz), 6.74 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H), 4.19 (s, 4H); LCMS: ret. time: 27.18 min.; purity: 95 %; MS (m/e): 490 ($MH^+$).

### 7.3.1117 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine (R925813)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and (4-methoxycarbonylphenyl)boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 26.35 min.; purity: 90 %; MS (m/e): 514 ($MH^+$).

### 7.3.1118 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine (R925816)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-hydroxyphenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR (DMSO-d6): δ 9.53 (s, 1H), 8.92 (s, 1H), 7.78 (s, 1H), 7.74 (bs, 1H), 7.24 (bs, 1H), 7.22 (d, 2H, J= 8.7 Hz), 7.12-7.09 (m, 2H), 6.97 (dt, 1H, J= 2.4 and 8.7 Hz), 6.83 (d, 2H, J= 8.4 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.62 (d, 1H, J= 9.0 Hz), 4.19 (s, 4H), 4.17 (s, 4H); LCMS: ret. time: 23.51 min.; purity: 95 %; MS (m/e): 471 ($MH^+$).

### 7.3.1119 N2,N4-Bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925783)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-

hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.85 (bs, 1H), 7.54-7.38 (m, 5H), 7.13-7.11 (m, 2H). 7.10-7.04 (m, 3H), 6.97 (dt, 1H, J= 1.8 and 8.1 Hz), 6.54 (ddd, 1H, J= 1.9, 2.4, and 7.2 Hz), 6.44 (dt, 1H, J= 1.8 and 6.0 Hz); LCMS: ret. time: 20.66 min.; purity: 96 %; MS (m/e): 371 ($MH^+$).

#### 7.3.1120 N2,N4-Bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine (R925788)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3,4-methylenedioxyphenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.82 (s, 1H), 7.13-7.06 (m, 3H), 7.04-7.01 (m, 2H), 6.97 (dt, 1H, J= 1.2 and 8.7 Hz), 6.94-6.88 (m, 3H), 6.52 (ddd, 1H, J= 1.2, 2.4, and 6.9 Hz), 6.42 (dt, 1H, J= 2.1 and 7.5 Hz), 6.01 (s, 2H); LCMS: ret. time: 21.11 min.; purity: 99 %; MS (m/e): 415 ($MH^+$).

#### 7.3.1121 N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925811)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine. $^1$H NMR ($CD_3OD$): δ 7.97-7.92 (m, 2H), 7.46-7.43 (m, 3H), 7.35 (d, 1H, J= 2.7 Hz), 7.19 (d, 1H, J= 2.4 Hz), 7.07-7.00 (m, 2H), 6.75 (t, 2H, J= 8.7 Hz), 6.50 (s, 1H), 4.24-4.19 (m, 8H); LCMS: ret. time: 26.68 min.; purity: 97 %; MS (m/e): 455 ($MH^+$).

#### 7.3.1122 N2,N4-Bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925812)

In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine. LCMS: ret. time: 22.13 min.; purity: 90 %; MS (m/e): 371 ($MH^+$).

### 7.3.1123 N2-(3-Aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926747)

The hydrolysis of N2-(3-cyanomethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine gave N2-(3-aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.76 min.; purity: 93 %; MS (m/e): 412 ($MH^+$).

### 7.3.1124 N2,N4-Bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine (R926461)

The reaction of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2 equivalents of sodium methoxide in methanol gave the requisite compound, N2,N4-bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine. $^1H$ NMR ($D_2O$): δ 7.65 (bd, 1H), 7.00-6.90 (m, 2H), 6.71 (m, 2H), 6.55 (dd, 1H, J= 1.2 and 6.3 Hz), 6.31 (bd, 1H, J= 8.1 Hz), 6.23 (bd, 1H, J= 8.7 Hz); $^{19}F$ NMR ($D_2O$): - 47016; LCMS: ret. time: 15.68 min.; purity: 99%; MS (m/e): 313 ($MH^+$).

### 7.3.1125 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945169)

The reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and HCl in ethanol, followed by 1,3-diaminopropane in methanol at 100 °C gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine. $^1H$ NMR ($CD_3OD$): δ 2.05 (p, J= 5.7 Hz, 2H), 3.49 (t, J= 5.7 Hz, 4H), 4.84 (s, 2H), 6.56 (ddd, J= 2.1, 3.6 and 5.4 Hz, 1H), 6.93 (d, J= 9.0 Hz, 2H), 7.11-7.13 (m, 2H), 7.21 (m, 1H), 7.55 (d, J= 9.0 Hz, 2H), 7.87 (d, J= 3.9 Hz, 1H); $^{19}F$ NMR (282 MHz, $CD_3OD$): δ - 168.66; LCMS: ret. time: 12.77 min.; purity: 97.61%; MS (m/e): 409.08 ($MH^+$).

### 7.3.1126 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine (R926702)

N2-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine. $^1H$ NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 3.6 Hz), 7.37 (t, 1H, J= 2.4 Hz),

7.34 (d, 2H, J= 9.0 Hz), 7.14 (t, 1H, J= 8.1 Hz), 6.94 (bs, 1H), 6.90 (d, 2H, J= 9.0 Hz), 6.78 (dd, 1H, J= 2.4 and 8.4 Hz), 6.74 (d, 1H, J= 3.0 Hz), 6.62 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 4.67 (s, 2H), 4.02 (s, 2H), 1.25 (s, 6H); $^{19}$F NMR ($CDCl_3$): -47399; LCMS: ret. time: 13.82 min.; purity: 98%; MS (m/e): 425 (M+2H).

**7.3.1127 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)**

A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 ($MH^+$).

**7.3.1128 N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)**

The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 ($MH^+$).

**7.3.1129 N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)**

A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 10.30 (s, 1H), 10.13 (s, 1H), 8.22 (d, 1H, J= 5.3 Hz), 7.96 (d, 1H, J= 2.4 Hz), 7.71 (dd, J = 2.4, 9.0 Hz, 1H), 6.95-7.11

(m, 4H), 6.51 (m, 1H), 4.56 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 1.14 (j, J = 7.2 Hz, 3H); LCMS: purity: 96.8%; MS (m/e): 457.25 ($MH^+$).

**7.3.1130 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)**

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 ($MH^+$).

**7.3.1131 N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)**

A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 ($MH^+$).

**7.3.1132 N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)**

A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 ($MH^+$).

### 7.3.1133 N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)

A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 ($MH^+$).

### 7.3.1134 N4-(2,3-Dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)

A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 ($MH^+$).

### 7.3.1135 N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)

A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 ($MH^+$).

### 7.3.1136 N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)

The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10

equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 ($MH^+$).

### 7.3.1137 N4-(2,3-Dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)

A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 ($MH^+$).

### 7.3.1138 N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950349)

A solution of N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 ($MH^+$).

### 7.3.1139 N4-(2,3-Dihydro-4-O-methyloxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950356)

A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-

dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.5%; MS (m/e): 465.10 ($MH^+$).

**7.3.1140 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950368)**

A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 ($MH^+$).

**7.3.1141 N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950371)**

A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J= 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J= 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 ($MH^+$).

**7.3.1142 N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950372)**

A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min

followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 ($MH^+$).

#### 7.3.1143 N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)

A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 ($MH^+$).

#### 7.3.1144 N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)

A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 ($MH^+$).

#### 7.3.1145 N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 ($MH^+$).

### 7.3.1146 N2,N4-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e): 489.29 ($MH^+$).

### 7.3.1147 N2,N4-Bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)

A solution of N2,N4-bis(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J= 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50 ($MH^+$).

### 7.3.1148 N2,N4-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)

A mixture of N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).

### 7.3.1149 N2,N4-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)

A mixture of N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 ($M-H^-$).

### 7.3.1150 N2,N4-Bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)

A mixture of N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 ($M-H^-$).

### 7.3.1151 N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).

### 7.3.1152 N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 ($MH^+$).

### 7.3.1153 N4-(4-Benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with bortrifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1$H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H) 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 ($M-H^-$).

### 7.3.1154 N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)

A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethylene oxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 ($MH^+$).

### 7.3.1155 N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950388)

A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 ($MH^+$).

### 7.3.1156 N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950389)

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was

treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 ($M-H^-$).

**7.3.1157 N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)**

A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. $^1H$ NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J= 7.2 Hz), 7.31 (d, 1H, J= 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 ($MH^+$).

**7.3.1158 N4-(3-Methoxycarbonyl-4-trifluoro methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)**

A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.8%; MS (m/e): 510.41 ($MH^+$).

**7.3.1159 N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)**

A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. $^1H$

NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$). LCMS: purity: 96.2%; MS (m/e): 479.13 ($M-H^-$).

**7.3.1160 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine HCl salt (R950399)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous HCl. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the HCl salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.2%; MS (m/e): 438.98 ($MH^+$).

**7.3.1161 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine succinic acid salt (R950400)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of succinic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the succinic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 438.98 ($MH^+$).

**7.3.1162 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine maleic acid salt (R950401)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of maleic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the maleic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-

methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 ($MH^+$).

**7.3.1163 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine fumaric acid salt (R950402)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of fumaric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the fumaric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 ($MH^+$).

**7.3.1164 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine citric acid salt (R950403)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of citric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the citric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 ($MH^+$).

**7.3.1165 N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine $HNO_3$ salt (R950404)**

A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous $HNO_3$. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the nitric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.2%; MS (m/e): 438.98 ($MH^+$).

### 7.4 Synthesis of Prodrugs

Exemplary prodrugs according to structural formula (II) were synthesized as described below.

#### 7.4.1 N-2(4)-Acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926233)

A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, acetyl chloride (4 equivalents), pyridine (4 equivalents) in $CH_2Cl_2$ was stirred at room temperature for 48h. After an aqueous work up the residue was chromatographed on silica gel to give N-2(4)-acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. $^1H$ NMR ($CDCl_3$): δ 8.23 (d, 1H, J= 5.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.90-7.80 (m, 3H), 6.76 (m, 2H), 4.28 (bs, 4H), 2.10 (s, 3H); $^{19}F$ NMR ($CDCl_3$): -42125; LCMS: ret. time: 27.94 min.; purity: 99%; MS (m/e): 439 ($MH^+$).

#### 7.4.2 N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 17.03 min.; purity: 87.0%; MS (m/e): 478.89 ($MH^+$).

#### 7.4.3 N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 ($MH^+$).

### 7.4.4 N4-(3-N-Acetylaminophenyl)-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-[3-N-acetylaminophenyl]-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97 ($MH^+$).

### 7.4.5 N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)

N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 ($MH^+$).

## 7.5 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit FcεRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit IgE-induced degranulation was demonstrated in a variety of cellular assays with cultured human mast cells (CHMC) and/or mouse bone marrow derived cells (BMMC). Inhibition of degranulation was measured at both low and high cell density by quantifying the release of the granule specific factors tryptase, histamine and hexosaminidase. Inhibition of release and/or synthesis of lipid mediators was assessed by measuring the release of leukotriene LTC4 and inhibition of release and/or synthesis of cytokines was monitored by quantifying TNF-α, IL-6 and IL-13. Tryptase and hexosaminidase were quantified using fluorogenic substrates as described in their respective examples. Histamine, TNFα, IL-6, IL-13 and LTC4 were quantified using the following commercial ELISA kits: histamine (Immunotech #2015, Beckman Coulter), TNFα (Biosource #KHC3011), IL-6 (Biosource #KMC0061),

IL-13 (Biosource #KHC0132) and LTC4 (Cayman Chemical #520211). The protocols of the various assays are provided below.

### 7.5.1 Culturing of Human Mast and Basophil Cells

Human mast and basophil cells were cultured from CD34-negative progenitor cells as described below (see also the methods described in copending U.S. application Serial No. 10/053,355, filed November 8, 2001, the disclosure of which is incorporated herein by reference).

#### 7.5.1.1 Preparation of STEMPRO-34 Complete Medium

To prepare STEMPRO-34 complete medium ("CM"), 250 mL STEMPRO-34™ serum free medium ("SFM"; GibcoBRL, Catalog No. 10640) was added to a filter flask. To this was added 13 mL STEMPRO-34 Nutrient Supplement ("NS"; GibcoBRL, Catalog No. 10641) (prepared as described in more detail, below). The NS container was rinsed with approximately 10 mL SFM and the rinse added to the filter flask. Following addition of 5 mL L-glutamine (200 mM; Mediatech, Catalog No. MT 25-005-CI and 5 mL 100X penicillin/streptomycin ("pen-strep"; HyClone, Catalog No. SV30010), the volume was brought to 500 mL with SFM and the solution was filtered.

The most variable aspect of preparing the CM is the method by which the NS is thawed and mixed prior to addition to the SFM. The NS should be thawed in a 37° C water bath and swirled, not vortexed or shaken, until it is completely in solution. While swirling, take note whether there are any lipids that are not yet in solution. If lipids are present and the NS is not uniform in appearance, return it to the water bath and repeat the swirling process until it is uniform in appearance. Sometimes this component goes into solution immediately, sometimes after a couple of swirling cycles, and sometimes not at all. If, after a couple of hours, the NS is still not in solution, discard it and thaw a fresh unit. NS that appears non-uniform after thaw should not be used.

#### 7.5.1.2 Expansion of CD34+ Cells

A starting population of CD34-positive (CD34+) cells of relatively small number (1-5 x $10^6$ cells) was expanded to a relatively large number of CD34-negative progenitor cells (about 2-4 x $10^9$ cells) using the culture media and methods described below. The CD34+ cells (from a single donor) were obtained from Allcells (Berkeley, CA). Because there is a degree of variation in the quality and number of CD34+ cells that Allcells

typically provides, the newly delivered cells were transferred to a 15 mL conical tube and brought up to 10 mL in CM prior to use.

On day 0, a cell count was performed on the viable (phase-bright) cells and the cells were spun at 1200 rpm to pellet. The cells were resuspended to a density of 275,000 cells/mL with CM containing 200 ng/mL recombinant human Stem Cell Factor ("SCF"; Peprotech, Catalog No. 300-07) and 20 ng/mL human flt-3 ligand (Peprotech, Catalog No. 300-19) ("CM/SCF/flt-3 medium"). On about day 4 or 5, the density of the culture was checked by performing a cell count and the culture was diluted to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium. On about day 7, the culture was transferred to a sterile tube and a cell count was performed. The cells were spun at 1200 rpm and resuspended to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium.

This cycle was repeated, starting from day 0, a total of 3-5 times over the expansion period.

When the culture is large and being maintained in multiple flasks and is to be resuspended, the contents of all of the flasks are combined into a single container prior to performing a cell count. This ensures that an accurate cell count is achieved and provides for a degree of uniformity of treatment for the entire population. Each flask is checked separately for contamination under the microscope prior to combining to prevent contamination of the entire population.

Between days 17-24, the culture can begin to go into decline (*i.e.*, approximately 5-10% of the total number of cells die) and fail to expand as rapidly as before. The cells are then monitored on a daily basis during this time, as complete failure of the culture can take place in as little as 24 hours. Once the decline has begun, the cells are counted, spun down at 850 rpm for 15 minutes, and resuspended at a density of 350,000 cells/mL in CM/SCF/flt-3 medium to induce one or two more divisions out of the culture. The cells are monitored daily to avoid failure of the culture.

When greater than 15% cell death is evident in the progenitor cell culture and some debris is present in the culture, the CD34-negative progenitor cells are ready to be differentiated.

#### 7.5.1.3 Differentiation of CD34-Negative Progenitor Cells into Mucosal Mast Cells

A second phase is performed to convert the expanded CD34-negative progenitor cells into differentiated mucosal mast cells. These mucosal cultured human mast

cells ("CHMC") are derived from CD34+ cells isolated from umbilical cord blood and treated to form a proliferated population of CD34-negative progenitor cells, as described above. To produce the CD43-negative progenitor cells, the resuspension cycle for the culture was the same as that described above, except that the culture was seeded at a density of 425,000 cells/mL and 15% additional media was added on about day four or five without performing a cell count. Also, the cytokine composition of the medium was modified such that it contained SCF (200 ng/mL) and recombinant human IL-6 (200 ng/mL; Peprotech, Catalog No. 200-06 reconstituted to 100 ug/mL in sterile 10 mM acetic acid) ("CM/SCF/IL-6 medium").

Phases I and II together span approximately 5 weeks. Some death and debris in the culture is evident during weeks 1-3 and there is a period during weeks 2-5 during which a small percentage of the culture is no longer in suspension, but is instead attached to the surface of the culture vessel.

As during Phase I, when the culture is to be resuspended on day seven of each cycle, the contents of all flasks are combined into a single container prior to performing a cell count to ensure uniformity of the entire population. Each flask is checked separately for contamination under the microscope prior to combining to prevent contamination of the entire population.

When the flasks are combined, approximately 75% of the volume is transferred to the communal container, leaving behind about 10 mL or so in the flask. The flask containing the remaining volume was rapped sharply and laterally to dislodge the attached cells. The rapping was repeated at a right angle to the first rap to completely dislodge the cells.

The flask was leaned at a 45 degree angle for a couple of minutes before the remaining volume was transferred to the counting vessel. The cells were spun at 950 rpm for 15 min prior to seeding at 35-50 mL per flask (at a density of 425,000 cells/mL).

#### 7.5.1.4 Differentiation of CD34-Negative Progenitor Cells into Connective Tissue-Type Mast Cells

A proliferated population of CD34-negative progenitor cells is prepared as above and treated to form a tryptase/chymase positive (connective tissue) phenotype. The methods are performed as described above for mucosal mast cells, but with the substitution of IL-4 for IL-6 in the culture medium. The cells obtained are typical of connective tissue mast cells.

#### 7.5.1.5 Differentiation of CD34-Negative Progenitor Cells into Basophil Cells

A proliferated population of CD34-negative progenitor cells is prepared as described in Section 6.4.1.2, above, and used to form a proliferated population of basophil cells. The CD34-negative cells are treated as described for mucosal mast cells, but with the substitution of IL-3 (at 20-50 ng/mL) for IL-6 in the culture medium.

### 7.5.2 CHMC Low Cell Density IgE Activation: Tryptase and LTC4 Assays

To duplicate 96-well U-bottom plates (Costar 3799) add 65 ul of compound dilutions or control samples that have been prepared in MT [137 mM NaCl, 2.7 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2$, 5.6 mM Glucose, 20 mM Hepes (pH 7.4), 0.1% Bovine Serum Albumin, (Sigma A4503)] containing 2% MeOH and 1% DMSO. Pellet CHMC cells (980 rpm, 10 min) and resuspend in pre-warmed MT. Add 65 ul of cells to each 96-well plate. Depending on the degranulation activity for each particular CHMC donor, load 1000-1500 cells/well. Mix four times followed by a 1 hr incubation at 37°C. During the 1 hr incubation, prepare 6X anti-IgE solution [rabbit anti-human IgE (1 mg/ml, Bethyl Laboratories A80-109A) diluted 1:167 in MT buffer]. Stimulate cells by adding 25 ul of 6X anti-IgE solution to the appropriate plates. Add 25 ul MT to un-stimulated control wells. Mix twice following addition of the anti-IgE. Incubate at 37°C for 30 minutes. During the 30 minute incubation, dilute the 20 mM tryptase substrate stock solution [(Z-Ala-Lys-Arg-AMC·2TFA; Enzyme Systems Products, #AMC-246)] 1:2000 in tryptase assay buffer [0.1 M Hepes (pH 7.5), 10 % w/v Glycerol, 10 uM Heparin (Sigma H-4898) 0.01% $NaN_3$]. Spin plates at 1000 rpm for 10 min to pellet cells. Transfer 25 ul of supernatant to a 96-well black bottom plate and add 100 ul of freshly diluted tryptase substrate solution to each well. Incubate plates at room temperature for 30 min. Read the optical density of the plates at 355nm/460nm on a spectrophotometric plate reader.

Leukotriene C4 (LTC4) is also quantified using an ELISA kit on appropriately diluted supernatant samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

### 7.5.3 CHMC High Cell Density IgE Activation: Degranulation (Tryptase, Histamine), Leukotriene (LTC4), and Cytokine (TNFalpha, IL-13) Assays

Cultured human mast cells (CHMC) are sensitized for 5 days with IL-4 (20 ng/ml), SCF (200 ng/ml), IL-6 (200 ng/ml), and Human IgE (CP 1035K from Cortx Biochem, 100-500ng/ml depending on generation) in CM medium. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at 1-2 x$10^6$ cells/ml in MT buffer. Add 100 ul of cell suspension to each well and 100 ul of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% $CO_2$) for 1 hour. After 1hour of compound treatment, stimulate cells with 6X anti-IgE. Mix wells with the cells and allow plates to incubate at 37°C (5% $CO_2$) for one hour. After 1 hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 ul per well of the supernatant, being careful not to disturb pellet. Place the supernatant plate on ice. During the 7-hour step (see next) perform tryptase assay on supernatant that had been diluted 1:500. Resuspend cell pellet in 240 ul of CM media containing 0.5% DMSO and corresponding concentration of compound. Incubate CHMC cells for 7 hours at 37°C (5% $CO_2$). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 ul per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

### 7.5.4 BMMC High Cell Density IgE Activation: Degranulation (Hexosiminidase, Histamine), Leukotriene (LTC4), and Cytokine (TNFalpha, IL-6) Assays

#### 7.5.4.1 Preparation of WEHI-Conditioned Medium

WEHI-conditioned medium was obtained by growing murine myelomonocytic WEHI-3B cells (American Type Culture Collection, Rockville, MD) in Iscove's Modified Eagles Media (Mediatech, Hernandon, VA) supplemented with 10% heat-inactivated fetal bovine serum (FBS; JRH Biosciences, Kansas City, MO), 50 μM 2-mercaptoethanol (Sigma, St. Louis, MO) and 100 IU/mL penicillin-steptomycin (Mediatech) in a humidified 37°C, 5% $CO_2$/95% air incubator. An initial cell suspension was seeded at 200,000 cells/mL and then split 1:4 every 3-4 days over a period of two weeks. Cell-free supernatants were harvested, aliquoted and stored at -80°C until needed.

### 7.5.4.2 Preparation of BMMC Medium

BMMC media consists of 20% WEHI-conditioned media, 10% heat-inactivated FBS (JHR Biosciences), 25 mM HEPES, pH7.4 (Sigma), 2mM L-glutamine (Mediatech), 0.1 mM non-essential amino acids (Mediatech), 1mM sodium pyruvate (Mediatech), 50 μM 2-mercaptoethanol (Sigma) and 100 IU/mL penicillin-streptomycin (Mediatech) in RPMI 1640 media (Mediatech). To prepare the BMMC Media, all components are added to a sterile IL filter unit and filtered through a 0.2 μm filter prior to use.

### 7.5.4.3 Protocol

Bone marrow derived mast cells (BMMC) are sensitized overnight with murine SCF (20 ng/ml) and monoclonal anti-DNP (10 ng/ml, Clone SPE-7, Sigma # D-8406) in BMMC media at a cell density of 666 $x10^3$ cells/ml. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at 1-3 $x10^6$ cells/ml in MT buffer. Add 100 ul of cell suspension to each well and 100 ul of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% $CO_2$) for 1 hour. After 1hour of compound treatment, stimulate cells with 6X stimulus (60 ng/ml DNP-BSA). Mix wells with the cells and allow plates to incubate at 37°C (5% $CO_2$) for one hour. After 1hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 ul per well of the supernatant, being careful not to disturb pellet, and transfer to a clean tube or 96-well plate. Place the supernatant plate on ice. During the 4-5 hour step (see next) perform the hexosiminidase assay. Resuspend cell pellet in 240 ul WEI-conditioned media containing 0.5% DMSO and corresponding concentration of compound. Incubate BMMC cells for 4-5 hours at 37°C (5% $CO_2$). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 ul per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

Hexosaminidase assay: In a solid black 96-well assay plate, add 50 uL hexosaminidase substrate (4-methylumbelliferyl-N-acetyl-β-D-glucosaminide; 2mM) to each well. Add 50 uL of BMMC cell supernatant (see above) to the hexoseaminidase substrate, place at 37°C for 30 minutes and read the plate at 5, 10, 15, and 30 minutes on a spectrophotometer.

### 7.5.5 Basophil IgE or Dustmite Activation: Histamine Release Assay

The basophil activation assay was carried out using whole human peripheral blood from donors allergic to dust mites with the majority of the red blood cells removed by dextran sedimentation. Human peripheral blood was mixed 1:1 with 3% dextran T500 and RBCs were allowed to settle for 20-25min. The upper fraction was diluted with 3 volumes of D-PBS and cells were spun down for 10 min at 1500 rpm, RT. Supernatant was aspirated and cells were washed in an equal volume MT-buffer. Finally, cells were resuspended in MT-buffer containing 0.5% DMSO in the original blood volume. 80 uL cells were mixed with 20 uL compound in the presence of 0.5% DMSO, in triplicate, in a V-bottom 96-well tissue culture plate. A dose range of 8 compound concentrations was tested resulting in a 10-point dose response curve including maximum (stimulated) and minimum (unstimulated) response. Cells were incubated with compound for 1 hour at 37°C, 5% $CO_2$ after which 20 uL of 6x stimulus [1 ug/mL anti-IgE (Bethyl Laboratories) 667 au/mL house dustmite (Antigen Laboratories)] was added. The cells were stimulated for 30 minutes at 37°C, 5% $CO_2$. The plate was spun for 10 min at 1500 rpm at room temperature and 80 uL the supernatant was harvested for histamine content analysis using the histamine ELISA kit supplied by Immunotech. The ELISA was performed according to supplier's instructions.

### 7.5.6 Results

The results of low density CHMC assays (Section 6.4.3), the high density BMMC assays (Section 6.4.5) and the basophil assays (Section 6.4.6) are provided in TABLE 1. The results of the high density CHMC assays (Section 6.4.4) are provided in TABLE 2. In TABLES 1 and 2, all reported values are $IC_{50}$s (in μM). A value of "9999" indicates an $IC_{50}$> 10μM, with no measurable activity at a 10μM concentration. Most compounds tested had $IC_{50}$s of less than 10μM, with many exhibiting $IC_{50}$s in the sub-micromolar range.

## 7.6 The 2,4-Pyrimidinediamine Compounds Inhibit FcγRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit FcγRI-mediated degranulation was demonstrated with Compounds R921218, R921302, R921303, R940347, R920410, R927050, R940350, R935372, R920323, R926971 and

R940352 in assays similar to those described in Section 6.4, with the exception that the cells were not primed with IgE and were activated with rabbit anti-human IgG Fab fragment (Bethyl Laboratories, Catalog No. A80-105).

All of the compounds tested exhibited $IC_{50}$s in the sub micromolar range.

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# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R008951 | | | | | | | | | | | | | | |
| R008952 | | | | | | | | | | | | | | |
| R008953 | | | | | | | | | | | | | | |
| R008955 | | | | | | | | | | | | | | |
| R008956 | | | | | | | | | | | | | | |
| R008958 | | | | | | | | | | | | | | |
| R067934 | | | | | | | | | | | | | | |
| R067963 | | | | | | | | | | | | | | |
| R070153 | | | | | | | | | | | | | | |
| R070790 | 1.665 | 9999 | | | | | | | | | | | | |
| R070791 | | | | | | | | | | | | | | |
| R081166 | | | | | | | | | | | | | | |
| R088814 | | | | | | | | | | | | | | |
| R088815 | | | | | | | | | | | | | | |
| R091880 | | | | | | | | | | | | | | |
| R092788 | | | | | | | | | | | | | | |
| R908696 | 3.553 | | | | | | | | | | | | | |
| R908697 | 9999 | 9999 | | | | | | | | | | | | |
| R909236 | 0.996 | 9999 | | | | | | | | | | | | |
| R909237 | 9999 | 9999 | | | | | | | | | | | | |
| R909238 | 0.174 | 9999 | | | | | | | <0.22 | | <0.22 | 0.521 | 0.432 | <0.22 |
| R909239 | 0.264 | 9999 | | | | | | | | | | | | |
| R909240 | 0.262 | 9999 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R909241 | 0.181 | 9999 | | | | | | | <0.22 | | <0.22 | 1.021 | 0.253 | <0.22 |
| R909242 | 0.567 | 9999 | | | | | | | | | | | | |
| R909243 | 0.263 | >10 | | | | | | | | | | | | |
| R909245 | 0.255 | 6.242 | | | | | | | | | | | | |
| R909246 | 0.169 | 9999 | | | | | | | | | | | | |
| R909247 | 2.393 | 9999 | | | | | | | | | | | | |
| R909248 | 3.582 | 9999 | | | | | | | | | | | | |
| R909249 | 9999 | 9999 | | | | | | | | | | | | |
| R909250 | 8.025 | 9999 | | | | | | | | | | | | |
| R909251 | 0.138 | 9999 | | | | | | | | | | | | |
| R909252 | 0.248 | 9999 | | | | | | | | | | | | |
| R909253 | 7.955 | 9999 | | | | | | | | | | | | |
| R909254 | 0.136 | 9999 | | | | | | | | | | | | |
| R920664 | 9999 | 9999 | | | | | | | | | | | | |
| R920665 | 1.1 | 9999 | | | | | | | | | | | | |
| R920666 | 2.53 | 9999 | | | | | | | | | | | | |
| R920668 | 3.2 | 9999 | | | | | | | | | | | | |
| R920669 | 0.42 | 9999 | | | | | | | | | | | | |
| R920670 | 2.18 | 9999 | | | | | | | | | | | | |
| R920671 | 9999 | 9999 | | | | | | | | | | | | |
| R920672 | 9999 | 9999 | | | | | | | | | | | | |
| R920818 | 9999 | 9999 | | | | | | | | | | | | |
| R920819 | 10 | 9999 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R920820 | 9999 | 9999 | | | | | | | | | | | | |
| R920846 | 9999 | 9999 | | | | | | | | | | | | |
| R920860 | 1.009 | 9999 | | | | | | | | | | | | |
| R920861 | 0.598 | >10 | | | | | | | | | | | | |
| R920893 | 1.239 | 9999 | | | | | | | | | | | | |
| R920894 | 0.888 | 5.566 | | | | | | | | | | | | |
| R920910 | 0.751 | 7.922 | | | | | | | | | | | | |
| R920917 | 1.579 | 9.729 | | | | | | | | | | | | |
| R921218 | 0.499 | 9999 | 0.55 | 0.6 | 9999 | 0.24 | 9999 | 0.302 | 0.133 | 9999 | 0.203 | 0.766 | 0.274 | 0.100 |
| R921219 | 0.059 | 9999 | | | | 0.025 | 9999 | 0.020 | 0.069 | | 0.058 | 0.040 | 0.039 | 0.009 |
| R925734 | | | | 9.2 | >10 | | | | 9999 | 9999 | | | | |
| R925747 | 1.021 | 3.1 | | | | | | | 3.1 | | | | | |
| R925755 | 0.898 | 9999 | | | | | | | | | | | | |
| R925757 | 2.8 | 9999 | | | | | | | | | | | | |
| R925758 | 1.175 | 9999 | | | | | | | | | | | | |
| R925760 | 4.85 | 9999 | | | | | | | | | | | | |
| R925765 | 6.8 | 9999 | | | | | | | | | | | | |
| R925766 | 8.9 | 9999 | | | | | | | | | | | | |
| R925767 | 10 | | | | | | | | | | | | | |
| R925768 | 9999 | | | | | | | | | | | | | |
| R925769 | 9999 | | | | | | | | | | | | | |
| R925770 | 9999 | | | | | | | | | | | | | |
| R925771 | 0.5 | 2.8 | 0.22 | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R925772 | 9999 | 9999 | | | | | | | | | | | | |
| R925773 | 0.673 | 9999 | | | | | | | | | | | | |
| R925774 | 0.435 | 9999 | | | | | | | | | | | | |
| R925775 | 0.225 | 9999 | 0.2 | | | | | | | | | | | |
| R925776 | 2.1 | 9999 | | | | | | | | | | | | |
| R925778 | 0.225 | 9999 | 0.18 | | | | | | | | | | | |
| R925779 | 0.265 | 9999 | 0.19 | | | | | | | | | | | |
| R925783 | 2.9 | 9999 | | | | | | | | | | | | |
| R925784 | 3.2 | 9999 | | | | | | | | | | | | |
| R925785 | 2.5 | 9999 | | | | | | | | | | | | |
| R925786 | 1.85 | 9999 | | | | | | | | | | | | |
| R925787 | 9 | 9999 | | | | | | | | | | | | |
| R925788 | 2.4 | 9999 | | | | | | | | | | | | |
| R925790 | 9999 | 9999 | | | | | | | | | | | | |
| R925791 | 9999 | 9999 | | | | | | | | | | | | |
| R925792 | 6.25 | 9999 | | | | | | | | | | | | |
| R925794 | 9999 | 9999 | | | | | | | | | | | | |
| R925795 | 9999 | 9999 | | | | | | | | | | | | |
| R925796 | 2 | 9999 | | | | | | | | | | | | |
| R925797 | 0.85 | 9999 | 0.28 | | | | | | | | | | | |
| R925798 | 9999 | 9999 | | | | | | | | | | | | |
| R925799 | 9999 | 9999 | | | | | | | | | | | | |
| R925800 | 9999 | 9999 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R925801 | 9999 | 9999 | | | | | | | | | | | | |
| R925802 | 9999 | 9999 | | | | | | | | | | | | |
| R925803 | 9999 | 9999 | | | | | | | | | | | | |
| R925804 | 9999 | 9999 | | | | | | | | | | | | |
| R925805 | 9999 | 9999 | | | | | | | | | | | | |
| R925806 | 9999 | 9999 | | | | | | | | | | | | |
| R925807 | 9999 | 9999 | | | | | | | | | | | | |
| R925808 | 9999 | 9999 | | | | | | | | | | | | |
| R925810 | 9999 | 9999 | | | | | | | | | | | | |
| R925811 | 3.3 | 9999 | | | | | | | | | | | | |
| R925812 | 5.8 | 9999 | | | | | | | | | | | | |
| R925813 | 9999 | 9999 | | | | | | | | | | | | |
| R925814 | 9999 | 9999 | | | | | | | | | | | | |
| R925815 | 9999 | 9999 | | | | | | | | | | | | |
| R925816 | 6 | 9999 | | | | | | | | | | | | |
| R925819 | 9999 | 9999 | | | | | | | | | | | | |
| R925820 | 9999 | 9999 | | | | | | | | | | | | |
| R925821 | 9999 | 9999 | | | | | | | | | | | | |
| R925822 | 9999 | 9999 | | | | | | | | | | | | |
| R925823 | 9999 | 9999 | | | | | | | | | | | | |
| R925824 | 9999 | 9999 | | | | | | | | | | | | |
| R925837 | 9999 | 9999 | | | | | | | | | | | | |
| R925838 | 9999 | 9999 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R925839 | 9999 | 9999 | | | | | | | | | | | | |
| R925840 | 9999 | 9999 | | | | | | | | | | | | |
| R925841 | 9999 | 9999 | | | | | | | | | | | | |
| R925842 | 7.3 | 9999 | | | | | | | | | | | | |
| R925843 | 9999 | 9999 | | | | | | | | | | | | |
| R925844 | 5.1 | 9999 | | | | | | | | | | | | |
| R925845 | 2.3 | 9999 | | | | | | | | | | | | |
| R925846 | 9999 | 9999 | | | | | | | | | | | | |
| R925849 | 8.2 | 9999 | | | | | | | | | | | | |
| R925851 | 0.925 | 9999 | | | | | | | | | | | | |
| R925852 | 3 | 9999 | | | | | | | | | | | | |
| R925853 | 9999 | 9999 | | | | | | | | | | | | |
| R925854 | 9999 | 9999 | | | | | | | | | | | | |
| R925855 | 4.2 | 9999 | | | | | | | | | | | | |
| R925856 | 9.85 | 9999 | | | | | | | | | | | | |
| R925857 | 5.95 | 9999 | | | | | | | | | | | | |
| R925858 | 8.05 | 7.3 | | | | | | | | | | | | |
| R925859 | 9999 | 9999 | | | | | | | | | | | | |
| R925860 | 9999 | 9999 | | | | | | | | | | | | |
| R925861 | 9999 | 9999 | | | | | | | | | | | | |
| R925862 | 0.7 | 9999 | | | | | | | | | | | | |
| R925863 | 0.274 | 9999 | | | | | | | | | | | | |
| R925864 | 9999 | 9999 | | | | | | | | | | | | |

## TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R925865 | 9999 | 9999 | | | | | | | | | | | | |
| R926016 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926017 | | | | 1.43 | 9999 | 0.53 | 9999 | | 1.4 | 9.6 | | | | |
| R926018 | | | | | | 9999 | 10 | | 8.5 | 9999 | | | | |
| R926037 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926038 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926039 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926058 | | | | | | 9999 | 9999 | | 9999 | 9999 | | | | |
| R926064 | | | | 6.2 | | | | | 5.9 | 7.3 | | | | |
| R926065 | | | | 3.5 | | | | | 9999 | 9999 | | | | |
| R926068 | | | | >10 | | | | | 7.4 | 8.2 | | | | |
| R926069 | | | | 9.1 | | | | | 4.5 | 4.4 | | | | |
| R926072 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926086 | | | | | | 2.5 | 9999 | | 2.8 | 7.3 | | | | |
| R926108 | | | 0.76 | 0.787 | 6.4 | 0.95 | 9999 | | 0.9 | 9999 | | | | |
| R926109 | 0.538 | 5.5 | 0.73 | 0.55 | >10 | 0.15 | 9999 | | 0.6 | 3.2 | | | | |
| R926110 | 1.071 | 9999 | 1.42 | 1.2 | >10 | 0.3 | 9999 | | 1 | 4.5 | | | | |
| R926113 | 0.413 | | 0.49 | 0.413 | 9999 | 0.27 | 9999 | | 0.65 | 9999 | | | | |
| R926114 | | | | 3.427 | 8.1 | 1.7 | 10 | | 9999 | 9999 | | | | |
| R926145 | | | | 4.764 | >10 | | | | 2.4 | 8.8 | | | | |
| R926146 | | | 1.59 | 0.761 | 6.7 | | | | 1.35 | 5 | | | | |
| R926147 | | | | 1.899 | >10 | | | | 2 | 7.1 | | | | |
| R926206 | | | | | | >10 | >10 | | 6.6 | 8.6 | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926209 | | | | | | >10 | 9999 | | 10 | 9.1 | | | | |
| R926210 | 0.926 | 9999 | 0.8 | 700 | 9999 | 0.37 | >10 | | 0.6 | >10 | | | | |
| R926211 | 1.299 | 9.8 | | 2.7 | 9999 | 1.55 | >10 | | 3.9 | >10 | | | | |
| R926212 | 0.654 | 9999 | 0.45 | | | 0.5 | >10 | | 0.5 | 5 | | | | |
| R926213 | 1.639 | 5.5 | | | | 1.75 | >10 | | | | | | | |
| R926218 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926219 | | | | 1.102 | 6.7 | | | | 2.5. | 3.2 | | | | |
| R926220 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926221 | | | | 8.5 | | | | | 9.9 | 9999 | | | | |
| R926222 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926223 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926224 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926225 | | | | >10 | | | | | 9999 | 9999 | | | | |
| R926228 | | | | >10 | | | | | 9999 | | | | | |
| R926229 | | | | >10 | | | | | | | | | | |
| R926230 | | | | >10 | | | | | | | | | | |
| R926234 | | | | >10 | | | | | 9999 | | | | | |
| R926237 | 1.207 | 6.2 | | | | | | | 1.9 | | | | | |
| R926240 | 0.381 | 1.7 | 0.145 | | | | | | | | | | | |
| R926241 | 7 | 9999 | | | | | | | | | | | | |
| R926242 | 4.2 | 9999 | | | | | | | | | | | | |
| R926243 | 3.1 | 9999 | | | | | | | | | | | | |
| R926245 | 3.1 | 9.4 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926248 | 0.9 | 9999 | 0.76 | | | | | | | | | | | |
| R926249 | 0.5 | 9999 | 0.25 | | | | | | | | | | | |
| R926252 | 2.8 | | | | | | | | | | | | | |
| R926253 | 0.8 | | 0.675 | | | | | | | | | | | |
| R926254 | 1.3 | 4 | | | | | | | | | | | | |
| R926255 | 1.4 | 4.5 | | | | | | | | | | | | |
| R926256 | 0.275 | 5.1 | 0.23 | | | | | | | | | | | |
| R926257 | 1.5 | 7.5 | | | | | | | | | | | | |
| R926258 | 0.9 | 9999 | 0.59 | | | | | | | | | | | |
| R926259 | 2.5 | 6.2 | | | | | | | | | | | | |
| R926319 | 9999 | 9999 | | | | | | | | | | | | |
| R926320 | 9999 | 9999 | | | | | | | | | | | | |
| R926321 | 9999 | 9999 | | | | | | | | | | | | |
| R926325 | 9999 | 9999 | | | | | | | | | | | | |
| R926331 | 9999 | 9999 | | | | | | | | | | | | |
| R926339 | 0.66 | 9999 | | | | | | | | | | | | |
| R926340 | 3.23 | 9999 | | | | | | | | | | | | |
| R926341 | 0.875 | 9999 | | | | | | | | | | | | |
| R926342 | 10 | 9999 | | | | | | | | | | | | |
| R926376 | 9999 | | | | | | | | | | | | | |
| R926386 | 9999 | 9999 | | | | | | | | | | | | |
| R926387 | 0.65 | 9999 | 0.7 | | | | | | | | | | | |
| R926394 | 9999 | 9999 | | | | | | | | | | | | |

# TABLE 1

| Test Compound | Low Density | | | CHMC anti-IgE Hexos. | CHMC Ionomycin Hexos. | Basophils anti-IgE Histamine | Basophils Ionomycin Histamine | Basophils Dust mite Histamine | High Density | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHMC anti-IgE Tryptase | CHMC Ionomycin Tryptase | CHMC anti-IgE LTC4 | | | | | | BMMC anti-IgE hexos | BMMC Ionomycin Hexos. | BMMC anti-IgE histamine | BMMC anti-IgE LTC4 | BMMC anti-IgE TNF-alpha | BMMC anti-IgE IL-6 |
| R926395 | 0.875 | 6.4 | 0.29 | | | | | | | | | | | |
| R926396 | 0.7 | 2.6 | 0.16 | | | | | | | | | | | |
| R926397 | 9999 | 9999 | | | | | | | | | | | | |
| R926398 | 9999 | 9999 | | | | | | | | | | | | |
| R926399 | 9999 | 9999 | | | | | | | | | | | | |
| R926400 | 9999 | 9999 | | | | | | | | | | | | |
| R926401 | 9999 | 9999 | | | | | | | | | | | | |
| R926402 | 9999 | 9999 | | | | | | | | | | | | |
| R926403 | 9999 | 9999 | | | | | | | | | | | | |
| R926404 | 9999 | 9999 | | | | | | | | | | | | |
| R926405 | 3.4 | 9999 | | | | | | | | | | | | |
| R926406 | 9999 | 9999 | | | | | | | | | | | | |
| R926408 | 9.6 | 9999 | | | | | | | | | | | | |
| R926409 | 3.15 | 9999 | | | | | | | | | | | | |
| R926411 | 0.69 | 2.5 | | | | | | | | | | | | |
| R926412 | 0.62 | 9999 | | | | | | | | | | | | |
| R926461 | 0.725 | 9999 | | | | | | | | | | | | |
| R926467 | 1.175 | 8.8 | | | | | | | | | | | | |
| R926469 | 9999 | | | | | | | | | | | | | |
| R926474 | 2.5 | 9999 | | | | | | | | | | | | |
| R926475 | 2.15 | >10 | | | | | | | | | | | | |
| R926476 | 0.6 | 7.7 | | | | | | | | | | | | |
| R926477 | 0.27 | 9999 | | | | | | | | | | | | |